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THEREOF

#### (57) Abstract

Compounds, compositions and methods involving purified, isolated and/or synthetic G-protein coupled receptor (GPR) polypeptides that comprise fragments, derivatives and/or consensus peptides of transmembrane domains of G-coupled receptor proteins, wherein the GPR polypeptide has biological activity selected from binding of a GPR ligand to a GPR or modulating the binding of GPR a ligand to a GPR.

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# POLYPEPTIDES OF G-COUPLED RECEPTOR PROTEINS, AND COMPOSITIONS AND METHODS THEREOF

#### FIELD OF THE INVENTION

The present invention relates to compounds, compositions and methods involving synthetic, isolated and/or recombinant G-protein coupled receptor polypeptides that comprise fragments and/or consensus peptides of G-protein coupled receptors.

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## BACKGROUND OF THE INVENTION

The membrane protein gene superfamily of G-protein coupled receptors (GPRs) has been characterized as having seven putative transmembrane domains. The domains are believed to represent transmembrane α-helices connected by extracellular or cytoplasmic loops. Of the 74 sequenced members of this G-protein receptor superfamily, the shortest sequence of 324 amino acids represents the rat mas oncogene and the longest, of 744 amino acids, represents the human thyroid-stimulating hormone (TSH) receptor. GPRs thus include a wide range of biologically active receptors, such as hormone-, viral-, growth factor- and neuroreceptors.

G-protein coupled receptors have been characterized as including these seven conserved hydrophobic stretches of about 20-30 amino acids, connecting at least 8 divergent hydrophilic loops. The G-protein family of coupled receptors includes dopamine receptors which bind in a noncovalent but high affinity manner to neuroleptic drugs used for treating psychotic and neurological disorders. For example, the dopamine  $D_2$  receptor includes these transmembrane domains, two of which (TM III and TM V; see below) have been implicated by site-selective mutagenesis to demonstrate functional, association with  $D_2$  ligands.

Transmembrane domains of G-protein coupled receptors are designated TM1, TM2, TM3, TM4, TM5, TM6 and TM7. TM4, TM5, TM6 and TM7 are the most highly conserved and are postulated to

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provide sequences which impart biological activity to GPRs. Most GPRs have single conserved cysteine residues in each of the first two extracellular loops which form disulfide bonds that are believed to stabilize functional protein structure. TM3 is also implicated in signal transduction.

Phosphorylation and lipidation (palmitylation or farnesylation) of cysteine residues can influence signal transduction of some GPRs. Most GPRs contain potential phosphorylation sites (e.g., serine or theronine residues) within the third cytoplasmic loop and/or the carboxy terminus. For several GPRs, such as the  $\beta$ -adrenoreceptor, phosphorylation by protein kinase A and/or specific receptor kinases mediates receptor desensitization.

Non-limiting examples of GPRs include cAMP receptors, adenosine receptors,  $\beta$ -adrenergic receptors, muscarinic acetylcholine receptors,  $\alpha$ -adrenergic receptors, serotonin receptors (5-HT), histamine H2 receptors, thrombin receptors, kinin receptors, follicle stimulating hormone receptors, opsins and rhodopsins, odorant receptors, cytomegalovirus receptor, etc. See e.g., Probst et al DNA and Cell Biology 11:1-20(1992), which is entirely incorporated herein by reference.

The ligand binding sites of GPRs are believed to comprise a hydrophilic socket formed by several GPR transmembrane domains, which socket is surrounded by hydrophobic residues of the GPRs. The hydrophilic side of each GPR transmembrane helix is postulated to face inward and form the polar ligand binding site. TM3 has been implicated in several GPRs as having a ligand binding site, such as including the TM3 aspartate residue. Additionally, TM5 serines, a TM6 asparagine and TM6 or TM7 phenylalanines or tyrosines are also implicated in ligand binding.

GPRs can be intracellularly coupled by heterotrimeric G-proteins to various intracellular enzymes, ion channels and transporters. See, e.g., Johnson et al *Endoc. Rev.* 10:317-331(1989); and Birnbaumer et al *Biochem. Biophys. Acta* 1031:163-224(1990) which references are incorporated entirely herein by reference. GPR agonist binding catalyzes the exchange

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of GTP for GDP on the  $\alpha$ -subunit of the G-protein. Different G-protein  $\alpha$ -subunits preferentially stimulate particular effectors to modulate various biological functions in a cell. Phosphorylation of cytoplasmic residues of GPRs has been identified as an important mechanism for the regulation of G-protein coupling of some GPRs.

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As a non-limiting example of a GPR ligand, dopamine (3,4-dihydroxyphenethylamine) is a critical neurotransmitter in the central nervous system (e.g., in the substantia nigra, midbrain, and hypothalamus). Since the elucidation of the ascending mesolimbic and nigrostriatal pathways, these pathways have been found to be critical in the control of both motor initiation (nigrostriatal) behavior and affective (mesolimbic) behavior. The clinical efficacy of the major neuroleptic antipsychotic medications has been found to correlate with the respective affinities of these agents for the dopamine  $D_2$ receptor in the brain. A dopaminergic role in the symptomatology of the major psychoses has thus been hypothesized, although it is unclear if dopamine alone is etiological, (see, e.g., Davis et al. Am. J. Psych. 148:1474-1476 (1991)). Nonetheless, this hypothesis has served as a stimulus for current research in this area.

One model for studying possible interactions of G-protein coupled receptors with their ligands has emerged from site-directed mutagenesis and biochemical analysis of the  $\beta$ -adrenergic receptor, as well as from biophysical analysis of the interaction of retinal with opsin.

According to such a model, the binding of a GPR ligand to a G-protein coupled receptor involves multiple interactions between functional groups on the GPR ligand and residues within the hydrophophilic binding site of the receptor.

While a number of the amino acid residues in the dopamine  $D_2$  receptor have been postulated to participate in  $D_2$  ligand binding, based on results obtained from site-directed mutagenesis studies and photoaffinity labeling studies performed on the  $\beta$ -adrenergic receptor, such studies have failed to specifically determine which residues are actually involved in

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binding in the  $D_2$  system. Sibley et al. Soc. Neurosci. Abs. 17:36.10, 324.5, 324.6 (1991).

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The clinical use of neuroleptics has provided a means for treating patients suffering from psychotic disorders. Short-term use of neuroleptics is indicated in several types of psychotic disorders, e.g., acute psychotic episodes, regardless of type; exacerbations of schizophrenia; acute manic excitement while deferring use of lithium or awaiting onset of its effects; adjunctive therapy for major depression with prominent psychotic symptoms, or when an antidepressant or ECT alone is not successful; for agitation in delirium, dementia, or severe mental retardation while seeking to identify and treat the primary basis of the problem; in certain chronic, degenerative, or idiopathic neuropsychiatric disorders with dyskinesias, such as Huntington's disease or Gilles de la Tourette's syndrome; or for ballism or hemiballism; childhood psychoses or apparently allied conditions marked by severe agitation or aggressive behavior; miscellaneous medical indications, notably nausea and vomiting, or intractable hiccups.

Additionally, continuous long-term use of neuroleptics is indicated in many psychotic disorders, such  $\epsilon$ .s (for more than six months) (i) primary indications such as Schizophrenia, Paranoia b, Childhood psychoses, some degenerative or idiopathic neuropsychiatric disorders (notably, Huntington's disease and Gilles de la Tourette's syndrome); (ii) secondary indications such as extremely unstable manic-depressive or other episodic psychoses (unusual), otherwise unmanageable behavior symptoms in dementia, amentia, or other brain syndromes; and (iii) questionable indications such as chronic characterological disorders with schizoid, "borderline," or neurotic characteristics; substance abuse; or antisocial behavior, recurrent mood disorders. See, e.g., Baldessarini, Chemotherapy in Psychiatry, Revised and Enlarged Edition, Harvard University Press, Cambridge, MA, (1985), the contents of which is entirely incorporated herein by reference.

Neuroleptics are also referred to as Leuroplegics, psychoplegics, psycholeptics, antipsychotics and major

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tranquilizers, but are sometimes distinguished from nonneuroleptic anti-psychotics. Neuroleptics have recently been characterized as an agent that produces sedative or tranquilizing effects, and which also produces motor side effects, such as catalepsy or extrapyramidal symptomatology. Nonlimiting representative examples of neuroleptics include phenothiazine derivatives (e.g., chlorpromazine); thioxanthine derivatives (e.g., thiothixene); butyrophenone derivatives (e.g., haloperidol); dihydroindolone (e.g., molindone); dibenzoxazepine derivatives (e.g., loxapine); and "atypical" neuroleptics (e.g., sulpiride, remoxipiride pimozide and clozapine). See Berstein Clinical Pharmacology Littleton, Mass.: PSG Publishing (1978); Usdin et al Clinical Pharmacology in Psychiatry New York: Elsevier North-Holland (1981); and Baldessarini, supra, (1985); and , which references are herein entirely incorporated by reference.

The term "atypical neuroleptics" has been used to describe antipsychotic neuroleptics that produce few or no extrapyramidal side effects and which do not cause catalepsy in animals (See, e.g., Picket et al, Arch. Gen. Psychiatry 49:345 (May 1992). Alternatively, atypical neuroleptics, such as clozapine, have been described as those neuroleptics which have a higher affinity for  $D_4$  and  $D_1$  sites than for  $D_2$  sites (See, e.g., Davis et al Amer. J. Psych. 148:1474, 1476 (November 1991).

The long term use of all known anti-psychotics, such as neuroleptics or non-neuroleptic antipsychotics, has resulted in serious side effects, as present in Table I, such as persistent and poorly reversible motoric dysfunctions (e.g., tardive dyskinesia) in a significant number of patients. These side effects are especially prevalent in geriatric populations, and adequate pharmacological treatment of these debilitating motoric dysfunctions is not currently available. This problem has severely limited the long-term, clinical administration of these agents.

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## TABLE I Neurological Side Effects of Neuroleptic-Antipsychotic Drugs

Reaction	Features	Period of maximum ris	Proposed mechanism k	Treatment		
Acute dystonia	Spasm of muscles of tongue, face, neck, back; may mimic seizures; not hysterical	1-5 days	Dopamine excess? Acetylcholine excess?	Antiparkinsonism agents are diagnostic and curative (i.m. or i.v., then p.o.)		
Parkinsonism	Bradykinesia, rigidity, variable tremor, mask- facies, shuffling gait	5-30 days (rarely persists)	Dopamine blockade	Antiparkinsonism agents (p.o); dopamine agonists risky?		
Akathisia	Motor restlessness; patient may experience anxiety or agitation	5-60 days (commonly persists)	Unknown	Reduce dose or change drug low doses of propranolol;* antiparkinsonism agents or or benzodiazepines may help		
Tardive dyskinesia	Oral-facial dyskinesia; choreo-athetosis, some- times irreversible, rarely progressive	6-24 months (worse on withdrawal)	Dopamine excess?	Prevention best; treatment unsatisfactory; slow spontaneous remission		
"Rabbit" syndrome	Perioral tremor (late parkinsonism variant?); usually reversible	Months or years	Unknown	Antiparkinsonism agents; reduce dose of neuroleptic		
Malignant syndrome	Catatonia, stupor, fever, unstable pulse and blood pressure; myoglobinemia; can be fatal	Weeks	Unknown	Stop neuroleptic; antiparkinsonism agents usually fail; bromocriptine often helps; dantrolene variable; general supportive care crucial		

a. There may be an increased risk of hypotension on interacting high doses of propranolol with some antipsychotic agents; clonidine may also be effective at doses of 0.2-0.8 mg/day, but carries a high risk of hypotension (Zubenko et al., Psychiatry Res. 11:143, 1984).

In addition, clozapine, although apparently capable of producing less motor side effects, can cause irreversible, potentially fatal agranulocytosis in a minority of patients administered the drug. Such serious side effects limit the use of

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clozapine to patients who are resistant to treatment with other neuroleptics.

Antipsychotics have a variety of significant pharmacological effects, e.g., as presented in the following Tables II and III.

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Table II
Comparative Pharmacology of Neuroleptics

	Phenothiazine Derivative	Thioxanthene Derivative	Butyrophenone Derivative
Alkaloid Pharmacologic Actions	Chlorpromazine	Thiothixene	Haloperidol
Antipsychotic	Yes + +	Yes + +	Yes + + + +
Antiemetic	Yes + + +	Not tested	Yes + + +
Hypothermia	Yes +	Yes +	No
Hypotension	Yes + +	Yes + + +	+
Parkinsonism	Yes + +	Yes +	Yes + + + +
Antiadrenergic	Yes + +	Yes + + +	+
Anticholinergic	Yes +	Yes +	Negligible
Antihistaminic	Yes +	Negligible	Negligible
Releases NE, DA	No	No	No
Blocks DA	Yes + +	Yes +	Yes + + + +
Blocks NE	Yes + +	Yes + + +	Yes +
Central sympathetic suppressant	Yes + +	Yes +	Yes + + +

Table III

Comparative Pharmacology of Antipsychotics

Extrapyramidal	Sedation	Adrenergic Blockage	Reaction
Chlorpromazine	High	Moderate to high High Low Moderate Low to moderate	Moderate
Chlorprothixene	High		Low to moderate
Haloperidol	Low		High
Molindone	Moderate		Moderate to high
Loxapine	High		High

See Ebadi, PHARMACOLOGY, Little, Brown and Co., Boston, 61-65 (1985); Cattabeni et al Adv. Biochem. Psychopharmacology 24:275 (1980). Baldessarini, supra, which references are herein incorporated entirely by reference.

However, despite the fact that thousands of neurolepticor antipsychotic-type compounds have been synthesized and reported in the literature, such compounds which lack serious side effects and which have sufficient pharmacological activity, have not been disclosed.

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Alternative to dopamine receptor GPRs, as presented above, other neuroreceptor GPRs are involved in neurological pathologies, and drugs such as neuroreceptor GPR binding agents, presently used for treating these pathologies, also suffer from 5 similar side effects as those of neuroleptics, as presented above.

Other GPRs are also involved in receptor-related pathologies, such as hormone related GPRs involved in endocrine related pathologies.

Accordingly, there is a need to provide G-protein coupled 10 receptor binding agents, including neuroreceptor and endocrine receptor GPRs, which do not produce such deleterious and debilitating side effects as those produced by known agents, such as neuroleptics, which can be used for therapy or diagnosis of GPR related pathologies.

Citation of documents herein is not intended as an admission that any of the documents cited herein is pertinent prior art, or an admission that the cited documents are considered material to the patentabilty of the claims of the present application. All statements as to the date or representations as 20 to the contents of these documents are based on the information available to the applicant and does not constitute any admission as to the correctness of the dates or contents of these documents.

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#### SUMMARY OF THE INVENTION

It is therefore an object of the present invention to 25 overcome one or more deficiencies found in the related art.

It is another object of the present invention to provide non-naturally occurring synthetic, isolated and/or recombinant GPR polypeptides which are fragments, consensus fragments and/or sequences having conservative amino acid substitutions, of at 30 least one transmembrane domain of at least one G-protein coupled receptor, which polypeptides have been discovered to have receptor-like functional binding sites of neuroreceptor and endocrine GPRs, such that GPR polypeptides of the present invention may bind GPR ligands, or which may also modulate, 35 quantitatively or qualitatively, GPR ligand binding to GPRs.

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It is still another object of the present invention to provide GPR polypeptides and compositions that have only partially helical structures, in contrast to known characterized transmembrane domains of GPRs, such as, but not limited to, GPR transmembrane domains I-VII.

It is yet another object of the present invention to provide synthetic or recombinant GPR polypeptides, conservative substitution derivatives thereof, antibodies, anti-idiotype antibodies, compositions and methods that can be used as potential modulators of G-protein coupled receptor function, by binding to GPR ligands or modulate GPR ligand binding, due to their expected biological properties, which may be used in diagnostic, therapeutic and/or research applications.

It is a further object of the present invention is to
15 provide synthetic, isolated or recombinant polypeptides which are
designed to inhibit or mimic various GPRs or fragments thereof, as
receptor types and subtypes.

According to one aspect of the present invention, a synthetic or recombinant GPR polypeptide is provided that

20 comprises a GPR amino acid sequence of, e.g., at least 5, 10, 15 or 20 amino acids, substantially corresponding to at least one transmembrane domain, or fragment and/or consensus peptide thereof, of a G-protein coupled receptor, wherein at least 20 amino acids are preferred. In a preferred embodiment, the

25 polypeptide is (a) chemically synthesized and/or (b) obtained from a recombinant host cell or organism which expresses a recombinant nucleic acid encoding a GPR polypeptide, as defined herein.

In another preferred embodiment, the transmembrane domain is selected from at least one of TM1, TM2, TM3, TM4, TM5, TM6 or TM7, corresponding to transmembrane domains I, II, III, IV, V, VI and VII, respectively, of a GPR. In another preferred embodiment, the transmembrane domain is a dopamine receptor transmembrane domain selected from the group consisting of at least one of a  $D_1$ ,  $D_2$ ,  $D_3$ ,  $D_4$  and  $D_5$  dopamine receptor transmembrane domain. The transmembrane domain, e.g., may be selected from at least one of  $D_2$  receptor transmembrane domains III or V. In still another preferred embodiment, the GPR polypeptide amino acid sequence

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substantially corresponding to an amino acid sequence contained in at least one of Fig. 2 (SEQ ID NO:2), Fig. 3 (SEQ ID NO:3) or Fig. 5 (SEO ID NO:5).

In another aspect of the present invention, a GPR composition is provided, comprising a GPR polypeptide, or a pharmaceutically acceptable ester, ether, sulfate, carbonate, malate, glucuronide or salt thereof, the composition further comprising a pharmaceutically acceptable carrier and/or diluent.

In still another aspect of the present invention, a

10 method is provided for treating a subject suffering from a disease state involving a qualitative or quantitative pathological abnormality of a GPR protein or a biological molecule functionally associated therewith. Such biological molecule may be a membrane cytoplasmic protein, lipid, carbohydrate, saccharide, nucleoside or nucleotide mono-, di-, or tri-phosphate, an enzyme, a cofactor, a nucleic acid, a neurotransmitter, an ion, a carrier, a cell receptor, or any combination thereof.

In a preferred embodiment, the GPR protein is a dopamine receptor and the abnormality involves a dopamine related

20 pathology, wherein the method comprises administering an effective dopamine receptor modulating amount of a GPR polypeptide of the present invention. In another preferred embodiment, the transmembrane domain is a D<sub>2</sub> dopamine receptor domain and the disease state is a psychiatric disorder, such as schizophrenia or schiz affective disorder (see American Psychiatric Association, Revised Manual of Diagnostic and Statistical Criteria for Psychiatric Disorders (DSM-III-R), American Psychiatric Assoc.

Press, Washington, DC (1989)).

In another preferred embodiment, the GPR composition is administered as a pharmaceutical composition to provide a GPR polypeptide in an amount ranging from about 0.01  $\mu g$  to 100 mg/kg, and also preferably, about 10  $\mu g$  to 10 mg/kg. In another preferred embodiment, the administering is by oral, intravenous, intramuscular, parenteral or topical administration, including mucosal administration to the nasal mucosa or the oral mucosa, by aerosol, nebulizer or drop administration as non-limiting examples.

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Other objects of the invention will be apparent to skilled practitioners from the following detailed description and examples relating to the present invention.

## BRIEF DESCRIPTION OF THE FIGURES

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Figure 1 is the amino acid sequence of a control peptide (SEQ ID NO:1), which is hydrophobic in its properties, but does not correspond to a known GPR transmembrane domain.

Fig. 2 represents the amino acid sequence of a GPR transmembrane polypeptide, polypeptide II (SEQ ID NO:2), which corresponds to a portion of the dopamine  $D_2$  receptor transmembrane segment III.

Fig. 3 represents the amino acid sequence of a transmembrane polypeptide, polypeptide III (SEQ ID NO:3), corresponding to a consensus peptide of the dopamine D<sub>2</sub> receptor transmembrane domains I-VII.

Fig. 4 represents the amino acid sequence of a consensus sequence of transmembrane domains that is shortened to be less than the length required to span a lipid bilayer.

Fig. 5 represents a consensus amino acid sequence of transmembrane domain as a consensus peptide between dopamine receptors  $D_1$  and  $D_2$ .

Fig. 6 is a representation of a circular dichroism spectrum of a solution of the consensus polypeptide III (SEQ ID NO:3) of Fig. 3.

Fig. 7 is a graphical representation of radioligand binding assay data comparing control polypeptide II (SEQ ID NO:1) of Fig. 1, labeled as "II" and consensus polypeptide I (SEQ ID NO:3) of Fig. 3, labeled as "I".

Fig. 8A-G are a comparison listing of amino acid sequences of transmembrane domains and adjacent amino acid sequences of representative GPRs (SEQ ID NOS:6-79).

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## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention relates to G-protein coupled receptor (GPR) polypeptides which can be used to mimic naturally occurring or isolated GPRs, or to modulate the binding of GPR ligands to GPRs, such as inhibition or enhancement of binding. GPR polypeptides of the present invention can include GPR transmembrane domain fragments and/or consensus peptides thereof, of at least 4-10 amino acids in length, and/or corresponding sequences having conservative amino acid substitutions as

10 "substitution peptides", wherein the GPR polypeptide binds a GPR ligand or modulates the binding of a GPR ligand to a GPR in vitro, in vivo or in situ.

GPR polypeptides of the present invention can be synthesized or recombinantly produced, or optionally purified, to provide commercially useful amounts of GPR polypeptides for use in therapeutic, diagnostic or research applications, according to known method steps, see, e.g., Ausubel et al, eds. Current Protocols in Molecular Biology, Wiley Interscience, N.Y., (1987, 1992); and Sambrook et al, Molecular Cloning, A Laboratory Manual, 2nd edition, Vols. 1-3, Cold Spring Harbor Press, (1989), which references are herein entirely incorporated by reference.

Additionally, GPR polypeptides according to the present invention can be used to generate polyclonal and/or monoclonal antibodies, anti-idiotype antibodies thereto, or fragments

25 thereof, which may used for diagnostic and/or therapeutic applications, according to known method steps, see, e.g., Harlow and Lane, <a href="Antibodies: A Laboratory Manual">Antibodies: A Laboratory Manual</a>, Cold Spring Harbor Press (1988), which is herein entirely incorporated by reference.

antibodies (or fragments thereof) to GPR polypeptides have been unexpectedly discovered to quantitatively or qualitatively modulate G-protein coupled receptors, such that binding of GPR polypeptides or anti-idiotype antibodies (or fragments thereof) to G-protein coupled receptor ligands may be used for diagnostic research or therapeutic applications of the present invention. Such GPR polypeptides, antibodies or anti-idiotype antibodies of the present invention may therefore be used as modulators of

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G-protein coupled receptors, such as neuroreceptors or endocrine receptors, as non-limiting examples.

Binding of such GPR polypeptides, (including GPR fragments, consensus peptides, substitution derivatives and anti-5 idiotype antibody fragments) of the present invention may be used to treat symptoms of, and provide diagnosis and treatment for, pathologies related to GPRs. Such pathologies have been found to correlate with symptoms occurring in neurological, viral or endocrine pathologies. D2 receptor-related psychotic disorders, 10 including schizophrenia, now treated with neuroleptics, is a nonlimiting example thereof.

The use of synthetic or recombinant GPR polypeptides of the present invention can be preferable to the use of known drugs that bind G-protein coupled receptors, such as neuroleptics that 15 bind or inhibit the biological effect of binding to neuroreceptors as a non-limiting example. Such polypeptides are expected to have significantly less side effects than presently used drugs presently used for inhibiting such receptor binding including neuroleptics, as they would structurally mimic naturally occuring 20 GPRs and/or modulate ligand binding. Thus, GPR polypeptides are expected to have reduced side effects attributable to known foreign compound drugs, with less immunogenicity, and reduced potential for motoric side effects (e.g., extrapyramidal symptoms and/or tardive dyskinesia).

The present invention is also related to the production, by chemical synthesis or recombinant DNA technology, of GPR polypeptides, preferably as small as possible while still retaining sufficiently high affinity or interaction with G-protein coupled receptors to modulate, such as to inhibit or to enhance, 30 binding to such receptors by GPR ligands.

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GPR polypeptides of the present invention may include 5-10 to 50-150 amino acid fragments, consensus sequences or substitution sequences of GPRs, e.g., as presented in Fig. 8A-G (SEQ ID NOS:6-79) including, but not limited to, multiple dopamine 35 receptors, cAMP receptors, adenosine receptors,  $\beta$ -adrenergic receptors, muscarinic acetylcholine receptors,  $\alpha$ -adrenergic receptors, serotonin receptors (5-HT), histamine H2 receptors,

Pllicle stimulating hormone ht receptors, ptors, dopamine receptor, eptors, N-formyl receptors, ceptors, IL-8 receptors, ndothelin receptors, ptor, neuromedin B ve intestinal peptides, tors, thyrotropin-releasing s, neuromedin K receptors, mas oncogene gonadotropin receptors, ing hormone receptors, hduced receptors, thoracic aorta GPRs, and t least 80% with at least scribed herein. See, e.g., 20(1992), which is entirely pled receptor polypeptide" ention includes equence" which ne 10 to 50 amino acid known GPR or group of omology of at least 80%, 89, 90, 91, 92, 93, 94, lile maintaining GPR peptide of the present is naturally occurring but does not occur in nature. esent invention orane domain of a GPR or tides wherein the GPR amino in length, such as 5, 6, 18, 19, 20, 21, 22, 23, 34, 35, 36, 37, 38, 39,

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40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140 or 150 amino acids, or any range therein.

An amino acid or nucleic acid sequence of a GPR polypeptide of the present invention is said to "substantially correspond" to another amino acid or nucleic acid sequence, respectively, if the sequence of amino acids or nucleic acid in both molecules provides polypeptides having biological activity that is substantially similar, qualitatively or quantitatively, to the corresponding fragment of at least one GPR transmembrane domain, or which may be synergistic when two or more transmembrane domains, consensus sequences or homologs thereof are present.

Additionally or alternatively, such "substantially corresponding" sequences of GPR polypeptides include conservative amino acid or nucleotide substitutions, or degenerate nucleotide codon substitutions wherein individual amino acid or nucleotide substitutions are well known in the art.

Alternatively or additionally, substantially corresponding refers to GPR polypeptides having amino acid sequences having at least 80% homology or identity to an amino acid sequence of SEQ ID NO:1, such as 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% homology or identity.

Accordingly, GPR polypeptides of the present invention, or nucleic acid encoding therefor, include a finite set of

25 substantially corresponding sequences as substitution peptides or polynucleotides which can be routinely obtained by one of ordinary skill in the art, without undue experimentation, based on the teachings and guidance presented herein. For a detailed description of protein chemistry and structure, see Schulz, G.E.

30 et al., Principles of Protein Structure, Springer-Verlag, New York, 1978, and Creighton, T.E., Proteins: Structure and Molecular Properties, W.H. Freeman & Co., San Francisco, 1983, which are hereby incorporated by reference. For a presentation of nucleotide sequence substitutions, such as codon preferences, see

35 Ausubel et al, supra, at §§ A.1.1-A.1.24, and Sambrook et al,

supra, at Appendices C and D.

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Conservative substitutions of a GPR polypeptide of the present invention includes a variant wherein at least one amino acid residue in the polypeptide has been conservatively replaced by a different amino acid. Such substitutions preferably are made in accordance with the following list as presented in Table IV, which substitutions may be determined by routine experimentation to provide modified structural and functional properties of a synthesized polypeptide molecule, while maintaining the receptor binding, inhibiting or mimicking biological activity, as determined by known GPR receptor activity assays.

Table IV

Original Residue	Exemplary Substitution
Ala	Gly;Ser
Arg	Lys
Asn	Gln;His
Asp	Glu
Cys	Ser
Gln	Asn
Glu	Asp
Gly	Ala;Pro
His	Asn;Gln
Ile	Leu; Val
Leu	Ile;Val
Lys	Arg;Gln;Glu
<b>M</b> et	Leu;Tyr;Ile
Phe	Met;Leu;Tyr
Ser	Thr
Thr	Ser
Trp	Tyr
Tyr	Trp; Phe
Val	Ile;Leu

Alternatively, another group of substitutions of GPR polypeptides of the present invention are those in which at least one amino acid residue in the protein molecule has been removed and a different residue inserted in its place according to the following Table V. The types of substitutions which may be made in the protein or peptide molecule of the present invention may be based on analysis of the frequencies of amino acid changes between a homologous protein of different species, such as those presented in Table 1-2 of Schulz et al., supra and Figs. 3-9 of Creighton, supra.

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Based on such an analysis, alternative conservative substitutions are defined herein as exchanges within one of the following five groups:

#### TABLE V

Small aliphatic, nonpolar or slightly polar residues: Ala, Ser, 1. Thr (Pro, Gly);

Polar, negatively charged residues and their amides: Asp, Asn, 2. Glu, Gln;

Polar, positively charged residues: 3.

His, Arg, Lys; Large aliphatic, nonpolar residues: 4.

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Met, Leu, Ile, Val (Cys); and Large aromatic residues: Phe, Tyr, Trp. 5.

The three amino acid residues in parentheses above have special roles in protein architecture. Gly is the only residue lacking any side chain and thus imparts flexibility to the chain. This however tends to promote the formation of secondary structure 5 other than  $\alpha$ -helical. Pro, because of its unusual geometry, tightly It generally tends to promote  $\beta$ -turn-like constrains the chain. some cases Cys can be structures, capable although in participating in disulfide bond formation which is important in protein folding. Note the Schulz et al. would merge Groups 1 and 2, Note also that Tyr, because of its hydrogen bonding potential, has significant kinship with Ser, and Thr, etc.

Conservative amino acid substitutions according to the present invention, e.g., as presented above, are known in the art and would be expected to maintain biological and structural properties of the polypeptide after amino acid substitution. Most deletions and insertions, and substitutions according to the present invention are those which do not produce radical changes in the characteristics of the protein or peptide molecule. "Characteristics" is defined in a non-inclusive manner to define both changes in secondary structure, 20 e.g.  $\alpha$ -helix or  $\beta$ -sheet, as well as changes in physiological activity, e.g. in receptor binding assays.

However, when the exact effect of the substitution, deletion, or insertion is to be confirmed one skilled in the art will appreciate that the effect of the substitution or substitutions will be evaluated by routine screening assays, either immunoassays or bioassays to confirm biological activity, such as receptor binding or modulation of ligand binding to the corresponding GPR. See, e.g., Maranges et al., eds., for example, a substituted polypeptide

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typically is made by site-specific mutagenesis of the peptide molecule-encoding nucleic acid, expression of the mutant nucleic acid in recombinant cell culture, and, optionally, purification from the cell culture, for example, by immunoaffinity chromatography using a specific antibody on a chemically derivatized column or immobilized membranes or hollow fibers (to absorb the mutant by binding to at least one epitope).

A preferred use of this invention is the production, by chemical or recombinant DNA technology, of GPR polypeptides, 10 preferably as small as possible while still retaining sufficiently high affinity for binding to, or association with, GPRs. production of GPR polypeptides including smaller fragments or variants of such transmembrane domains, one skilled in the art, using known binding and inhibition assays, can readily identify the GPR 15 polypeptides capable of binding minimizing or modulating G-protein coupled receptors using known methods. Non-limiting examples of fragments of GPRs to be used as GPR polypeptides or as a basis for consensus sequences thereof for GPR polypeptides, are presented in Figs. 2-5 and Fig. 8A-G, wherein fragments or consensus sequences of 20 10 to 50 amino acids of at least one sequence of Figs. 2-5 or corresponding to at least one transmembrane domain or domains 1-7 listed in Fig. 8A-G (SEQ ID NOS:6-79) are encompassed by the present invention, such as at least one transmembrane domain of one or more GPRs, such as a cAMP receptor (1), adenosine receptors (2-3); 25 muscarinic acetylcholine receptors (4-8); human adrenergic receptors (9-11, 14-16, 19-25, 28); adrenergic receptors (9-28); human thrombin receptor (31); endothelin receptors (35-36), bombesin receptors (37-38), endocrine receptors (48-50), rhodopsin (51). opsins (52-54), odorant receptors (55-64), and cytomegalovirus GPRs (72-54), as non-30 limiting examples, wherein ("#") refers to the listed sequences in Fig. 8A-G.

Accordingly, GPR polypeptides may include consensus sequences and/or fragments of at least one of transmembrane domain 1-7 of one or more GPRs as presented in Figs. 2-5 (SEQ ID NO:2-5) or Fig. 8A-G. (SEQ ID NOS:6-79) or homologs thereof, which GPR polypeptides do not occur naturally, and/or which are provided in an isolated and/or purified form not found in nature.

Consensus peptides of GPR polypeptides of the present invention may include peptides which are distinct from known GPR sequences in critical structural features, but which are derived from consensus sequences of homologous GPR transmembrane domains 1-7. 5 e.g., as presented in Fig. 8A-G (SEQ ID NOS:6-79). Such consensus peptides may be derived by molecular modeling, optionally combined with hydrophobicity analysis and/or fitting to model helices, as non-limiting examples. Such modeling can be accomplished according to known method steps using known modeling algorithms, such as, but 10 not limited to, ECEPP, INSIGHT, DISCOVER, CHEM-DRAW, AMBER, FRODO and Such algorithms compare transmembrane domains between related G-protein coupled receptors, determine probable energymiminized structures and define alternative consensus polypeptide fragments.

Such consensus peptides or fragments of GPRs may then be synthesized or produced recombinantly, in order to provide GPR polypeptides according to the present invention which mimic, modulate or inhibit binding of ligands to G-protein coupled receptors. ligands, in the context of the present invention, refer to biological 20 molecules that bind GPRs in vitro, in situ or in vivo, and may include hormones, neurotransmitters, viruses or receptor binding domains, thereof, opsins, rhodopsins, nucleosides, nucleotides, coagulation cascade factors, odorants or pheremones, toxins, colony stimulating factors, platelet activating factors, neuroactive 25 peptides, neurohumors, or any biologically active compounds, such as drugs or synthetic or naturally occurring compounds.

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The following non-limiting examples of consensus peptides of GPRs of the present invention are provided by way of guidance and not by way of limitation. In GPR polypeptides of the present 30 invention, one or more, preferably 4-10, Asp and/or Lys residues may additionally be incorporated at the carboxy and/or amino terminal ends in order to provide expected helix forming effects of the helix dipole effect, e.g., as described in Baldwin et al Biochem. 28:2130 (1989); Baldwin et al Proc. Nat'l Acad. Sci. USA 84:8898 (1987); and 35 Baldwin et al Proc. Nat'l Acad. Sci. USA 86:5286 (1989), which references are entirely incorporated herein by reference.

As a non-limiting example of GPR polypeptide of the present invention, dopamine receptor transmembrane fragments of  $D_2$  transmembrane domain (e.g., domain III) as presented in Fig. 2 (SEQ ID NO:2) or a consensus sequence as presented in Fig. 3 (SEQ ID NO:3), e.g., of  $D_2$  domains I-VII. Additionally or alternatively a consensus sequence may include less than 20 amino acids, such as 15 amino acids corresponding to a transmembrane domain, such as a  $D_2$  receptor domain, as presented in Fig. 4 (SEQ ID NO:4) as polypeptide IV, which is smaller than the length required by spanning an average lipid bilayer of a cell membrane.

However, in the context of the present invention, GPR polypeptides of greater than 15 -20 amino acids are preferred such that the GPR polypeptides are able to span the lipid bilayer.

Another non-limiting example of a GPR polypeptide using dopamine receptor transmembrane domains is a consensus sequence of two or more GPR receptors, such as the dopamine  $D_1$  and  $D_2$  receptors. A non-limiting example of such a consensus GPR polypeptide is presented in Fig. 5 (SEQ ID NO:5).

Additionally, modified amino acids or chemical derivatives
of amino acids of consensus or fragments of GPRs proteins, according
to the present invention may be provided, which polypeptides contain
additional chemical moieties or modified amino acids not normally a
part of the protein. Covalent modifications of the peptide are thus
included within the scope of the present invention. Such
modifications may be introduced into a GPR polypeptide by reacting
targeted amino acid residues of the polypeptide with an organic
derivatizing agent that is capable of reacting with selected side
chains or terminal residues. The following examples of chemical
derivatives are provided by way of illustration and not by way of
limitation.

Aromatic amino acids may be replaced with D- or L-naphylalanine, D- or L-Phenylglycine, D- or L-2-thieneylalanine, D- or L-1-, 2-, 3- or 4-pyreneylalanine, D- or L-3-thieneylalanine, D- or L-(2-pyridinyl)-alanine, D- or L-(3-pyridinyl)-alanine, D- or L-(2-pyrazinyl)-alanine, D- or L-(4-isopropyl)-phenylglycine, D-(trifluoromethyl)-phenylglycine, D-p-fluorophenylalanine, D- or L-p-biphenylphenylalanine, D- or

L-p-methoxybiphenylphenylalanine, D- or L-2-indole(alkyl)alanines, and D- or L-alkylainines where alkyl may be substituted or unsubstituted methyl, ethyl, propyl, hexyl, butyl, pentyl, isopropyl, iso-butyl, sec-isotyl, iso-pentyl, non-acidic amino acids, 5 of C1-C20.

Acidic amino acids can be substituted with non-carboxylate amino acids while maintaining a negative charge, and derivatives or analogs thereof, such as the non-limiting examples of (phosphono)alanine, glycine, leucine, isoleucine, threonine, or serine; or 10 sulfated (e.g., -SO<sub>3</sub>H) threonine, serine, tyrosine.

Other substitutions may include unnatural hyroxylated amino acids may made by combining "alkyl" (as defined and exemplified herein) with any natural amino acid. Basic amino acids may be substituted with alkyl groups at any position of the naturally 15 occurring amino acids lysine, arginine, ornithine, citrulline, or (guanidino)-acetic acid, or other (guanidino)alkyl-acetic acids, where "alkyl" is define as above. Nitrile derivatives (e.g., containing the CN-moiety in place of COOH) may also be substituted for asparagine or glutamine, and methionine sulfoxide may be 20 substituted for methionine. Methods of preparation of such peptide derivatives are well known to one skilled in the art.

In addition, any amide linkage in any of the GPR polypeptides can be replaced by a ketomethylene moiety, e.g. (-C(=0)- $CH_{2}$ -) for (-(C=O)-NH-). Such derivatives are expected to have the 25 property of increased stability to degradation by enzymes, and therefore possess advantages for the formulation of compounds which may have increased in vivo half lives, as administered by oral, intravenous, intramuscular, intraperitoneal, topical, intraocular, or other routes.

In addition, any amino acid representing a component of the said peptides can be replaced by the same amino acid but of the opposite chirality. Thus, any amino acid naturally occurring in the L-configuration (which may also be referred to as the R or S, depending upon the structure of the chemical entity) may be replaced 35 with an amino acid of the same chemical structural type, but of the opposite chirality, generally referred to as the D- amino acid but which can additionally be referred to as the R- or the S-, depending

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upon its composition and chemical configuration. Such derivatives have the property of greatly increased stability to degradation by enzymes, and therefore are advantageous in the formulation of compounds which may have longer *in vivo* half lives, when administered by oral, intravenous, intramuscular, intraperitoneal, topical, rectal, intraocular, or other routes.

Additional amino acid modifications of amino acids of GPR polypeptides of to the present invention may include the following: Cysteinyl residues may be reacted with alpha-haloacetates (and amines), such as 2-chloroacetic 10 corresponding chloroacetamide, carboxymethyl or carboxyamidomethyl to give derivatives. Cysteinyl residues may also be derivatized by reaction bromotrifluoroacetone, alpha-bromocompounds such as with chloroacetyl beta-(5-imidozoyl)propionic acid, phosphate, 15 N-alkylmaleimides, 3-nitro-2-pyridyl disulfide, methyl 2-pyridyl disulfide, p-chloromercuribenzoate, 2-chloromercuri-4-nitrophenol, or chloro-7-nitrobenzo-2-oxa-1,3-diazole.

Histidyl residues may be derivatized by reaction with compounds such as diethylprocarbonate e.g., at pH 5.5-7.0 because this agent is relatively specific for the histidyl side chain, and para-bromophenacyl bromide may also be used; e.g., where the reaction is preferably performed in 0.1 M sodium cacodylate at pH 6.0.

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Lysinyl and amino terminal residues may be reacted with compounds such as succinic or other carboxylic acid anhydrides.

25 Derivatization with these agents is expected to have the effect of reversing the charge of the lysinyl residues. Other suitable reagents for derivatizing alpha-amino-containing residues include compounds such as imidoesters/e.g., as methyl picolinimidate; pyridoxal phosphate; pyridoxal; chloroborohydride; trinitrobenzenesulfonic acid; O-methylisourea; 2,4 pentanedione; and transaminase-catalyzed reaction with glyoxylate.

Arginyl residues may be modified by reaction with one or several conventional reagents, among them phenylglyoxal, 2,3-butanedione, 1,2-cyclohexanedione, and ninhydrin according to known method steps. Derivatization of arginine residues requires that the reaction be performed in alkaline conditions because of the high pKa of the guanidine functional group. Furthermore, these

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reagents may react with the groups of lysine as well as the arginine epsilon-amino group.

The specific modification of tyrosyl residues <u>per se</u> is well-known, such as for introducing spectral labels into tyrosyl residues by reaction with aromatic diazonium compounds or tetranitromethane. N-acetylimidizol and tetranitromethane may be used to form 0-acetyl tyrosyl species and 3-nitro derivatives, respectively.

Carboxyl side groups (aspartyl or glutamyl) may be selectively modified by reaction with carbodiimides (R' N-C-N-R') such as 1-cyclohexyl-3-(2-morpholinyl- (4-ethyl) carbodiimide or 1-ethyl-3-(4-azonia-4,4-dimethylpentyl) carbodiimide. Furthermore, aspartyl and glutamyl residues may be converted to asparaginyl and glutaminyl residues by reaction with ammonium ions.

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Glutaminyl and asparaginyl residues may be frequently deamidated to the corresponding glutamyl and aspartyl residues. Alternatively, these residues may be deamidated under mildly acidic conditions. Either form of these residues falls within the scope of the present invention.

Derivatization with bifunctional agents is useful for 20 cross-linking the peptide to a water-insoluble support matrix or to other macromolecular carriers, according to known method steps. agents cross-linking include, used Commonly 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, example, for 25 N-hydroxysuccinimide esters, 4-azidosalicylic acid, homobifunctional imidoesters, including a s 3 , 3 ' disuccinimidyl such esters dithiobis(succinimidylpropionate), and bifunctional maleimides such Derivatizing agents as bis-N-maleimido-1,8-octane. 30 methyl-3-[(p-azidophenyl)dithio]propioimidateyieldphotoactivatable intermediates that are capable of forming crosslinks in the presence of light. Alternatively, reactive water-insoluble matrices such as cyanogen bromide-activated carbohydrates and the reactive substrates described in U.S. Patent Nos. 3,969,287; 3,691,016; 4,195,128; 35 4,247,642; 4,229,537; and 4,330,440 (which are herein incorporated entirely by reference), may be employed for protein immobilization.

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Other modifications of GPR polypeptides of the present invention may include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the alpha-amino groups of lysine, arginine, and 5 histidine side chains (T.E. Creighton, Proteins: Molecule Properties, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)), acetylation of the N-terminal amine, methylation of main chain amide residues (or substitution with N-methyl amino acids) and, in some instances, amidation of the C-terminal carboxyl groups, 10 according to known method steps.

Such derivatized moieties may improve the solubility, absorption, permeability across the blood brain barrier biological half life, and the like. Such moieties or modifications of GPR polypeptides may alternatively eliminate or attenuate any possible 15 undesirable side effect of the protein and the like. capable of mediating such effects are disclosed for example, in Remington's Pharmaceutical Sciences, 16th ed., Mack Publishing Co., Easton, PA (1980).

Such chemical derivatives of GPR polypeptides also may provide attachment to solid supports, including but not limited to, agarose, cellulose, hollow fibers, or other polymeric carbohydrates such as agarose, cellulose, such as for purification, generation of antibodies or cloning; or to provide altered physical properties, such as resistance to enzymatic degradation or increased binding 25 affinity or modulation for GPRs, which is desired for therapeutic compositions comprising GPR polypeptides, antibodies thereto or fragments thereof. Such peptide derivatives are well-known in the art, as well as method steps for making such derivatives using carbodiimides active esters of N-hydroxy succinimmide, or mixed 30 anhydrides, as non-limiting examples.

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Variation upon consensus peptide sequences of polypeptide of the present invention may also include: the addition of one, two, three, four, or five lysine, arginine or other basic residues added to the -COOH terminal end of the peptide; and/or one, 35 two, three, four, or five glutamate or aspartate or other acidic residues added to the amino terminal end of the peptide, where "acidic" and "basic" are as defined herein. Such modifications are

well known to increase the  $\alpha$ -helical content of the peptide by the "helix dipole effect". They also can provide enhanced aqueous solubility of the peptide. See, e.g., Baldwin et al., <u>supra</u>

As another non-limiting example of a GPR polypeptide of the present invention, serotonergic receptors (5-HT) consensus sequences may be determined using presently known 5-HT sequences and include, e.g., as consensus peptides of TM3, TM5 and TM7, espectively:

- 5-HT consensus (1) DDDDNIWSIFDWIGYLNSISMVIYTLFKKKK (SEQ ID NO:80)
- 5-HT consensus (2) DDDDNIWNIFSTIGYLNSISPVSVIMHIYGKKKK (SEQ ID NO:81)
- 10 5-HT consensus (3) DDDDGYSIYDTLVTFAINPVYITVFKKKK (SEQ ID NO:82)

Such non-naturally occurring consensus sequences may also be further modified according to known method steps to provide additional consensus peptides with substituted amino acids to increase or decrease  $\alpha$ -helical propensity and/or solubility (e.g., hydrophilicity). As a non-limiting example, 5-HT consensus peptide (1) above may be modified according to the present invention to have increase helical propensity and increased aqueous solubility as follows:

5-HT consensus (4) DDDDNAWSAFDWALYLNSISMAIYTYAKKKK (SEQ ID NO:83),

wherein, e.g., smaller, non-polar residues replace either larger, more polar residues (e.g., Ala for Ile or Val) or larger aromatic residues (e.g., Ala for Phe).

Another non-limiting, illustrative example of consensus GPR polypeptides of the present invention are those for adrenergic receptors, are the following:

An example of the consensus GPR polypeptide for domain VII across all presently known adrenergic receptors is as follows:

adrenergic consensus(1) LFSFITWLGYANSSLNPIIYTTF (SEQ ID NO:84)

An example of a consensus GPR polypeptide for domain V across all adrenergic receptors is as follows:

adrenergic consensus(2) VYTIYSSSVVFFAPSLAIMVITYT (SEQ ID NO:85)

Examples of a consensus GPR polypeptide for domain III across all adrenergic receptors are as follows:

adrenergic consensus (3) IWLTSDIMSTSSILHNLCVISF (SEQ ID NO:86)

5 An example of a consensus GPR polypeptide for domains III, V, and VII of all adrenergic receptors is as follows:

adrenergic consensus(4) IWSIFSSDIVVGYANHSSLAIMCPIVIYTV (SEQ ID NO:87)

adrenergic consensus(5) IFTIFSSDIAVGYANHSSAAIMPIVIYSV (SEQ ID NO:88),

Wherein variations and substitutions of amino acids may be made as 10 described herein.

Non-limiting examples of consensus GPR polypeptides for transmembrane domain III across several or many, such as 1-500, or any range or value therein, G-protein receptors are as follows:

- TM3-(1) YAIFVLYASAWLSFLNCPFIVTLNI (SEQ ID NO:96)
- 15 TM3-(2) YAIFVLYATAWLSFLNCPFIVTLNI (SEQ ID NO:97)
  - TM3-(3) YAIFVLYATAWLTFLNCPFIVTLNI(SEQ ID NO:98)
  - TM3-(4) YAIFVLYASAWLTFLNCPFIVTLNI(SEQ ID NO:99)
  - 'IM3-(5) WAIFVLYASAWLSFLNCPFIVTLNI(SEQ ID NO:100)
  - TM3-(6) WAIFVLYATAWLSFLNCPFIVTLNI(SEQ ID NO:101)
- 20 TM3-(7) WAIFVLYATAWLTFLNCPFIVTLNI (SEQ ID NO:102)
  - TM3-(8) WAIFVLYASAWLTFLNCPFIVTLNI(SEQ ID NO:103)
  - TM3-(9) YAVFVLYASAWLSFLNMPFIVTLNI(SEQ ID NO:104)
  - TM3-(10) YAVFVLYATAWLSFLNMPFIVTLNI(SEQ ID NG:105)
  - TM3-(11) YAVFVLYATAWLTFLNMPFIVTLNI(SEQ ID NO:106)
- 25 TM3-(12) YAVFVLYASAWLTFLNMPFIVTLNI(SEQ ID NO:107)
  - TM3-(13) YAIFVLYASAWLSFLNCVTASIPFIVTLNI(SEQ ID NO:108)
  - TM3-(14) YAIFVLYASAWLSFLNCTSSIVVTASIVTLNI(SEQ ID NO:109)
  - TM3-(15) YAIFVLYASAWLSFLNVTLNICTSSIV (SEQ ID NO:110)
  - TM3-(16) YAIFVLYASAWLSFLNTASILNLMFIVTLNI(SEQ ID NO:111)
- 30 TM3-(17) YAIFVLYASAWLSFLNMASILNLPFIVTLNI (SEQ ID NO:112)
  - TM3-(18) YAIFVLYASAWLSFLNSGILLLAPFIVTLNI(SEQ ID NO:113)
  - TM3-(19) YAIFVLYASAWLSFLNMSGILLLAPFIVTLNI(SEQ ID NO:114)
  - TM3-(20) YAIFVLYASAWLSFLNSELSVYTLTVCPFIVTLNI(SEQ ID NO:115)
  - TM3 (21) YAIFVLYASAWLSFLNMSELSVYTLTVPFIVTLNI (SEQ ID NO:116)

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- TM3-(22) YAIFVLYASAWLASELSVYTLTVSFLNCPFIVTLNI(SEQ ID NO:117)
- TM3-(23) YAIFVLYASAWLASELSVYTLTVPFIVTLNI(SEQ ID NO:118)
- TM3-(24) YAIFVLYASAWLSFLASELSVYASELSSTLTTVNMPFIVTLNI(SEQ ID NO:119)
- TM3-(25) YAIFVLYASAWLSFLNGGEIALWSLCPFIVTLNI(SEQ ID NO:120)
- 5 TM3-(26) YAIFVLYASAWLSFLNGGEIALWSLIVTLNI(SEQ ID NO:121)
  - TM3-(27) YAIFVLYASAWLGGEIALWSLNCPFIVTLNI(SEQ ID NO:122)
  - TM3-(28) YAIFVLYAGGEIALWSLSFLNCPFIVTLNI(SEQ ID NO:123)
  - TM3-(29) YAIFVLYASAWLSFFFLLFGYLGNFLLNCPFIVTLNI(SEQ ID NO:124)
  - TM3-(30) YAIFVLYASAWLFFFLLFGYLGNFLLPFIVTLNI(SEQ ID NO:125)
- 10 TM3-(31) YAIFVLYASAWLSFLNTACFYVAITASLCFITEIALIPFIVTLNI(SEQ ID NO:126)
  - TM3-(32) YAIFVLYASAWLTACFYVAITASLCFITEIALICPFIVTLNI(SEQ ID NO:127)
  - TM3-(33) YAIFVLYATACFYVAITASLCFITEIALISFLNCPFIVTLNI(SEQ ID NO:128)
  - TM3-(34) YAITACFYVAITASLCFITEIALIASAWLSFLNCPFIVTLNI(SEQ ID NO:129)
  - TM3-(35) YAIFVLYATACFYVAIITEIALISAWLSFLNCPFIVTLNI(SEQ ID NO:130)
- 15 TM3-(36) YAIFVLYASAWLSFLNACFYICLFAGVCFLIPFIVTLNI(SEQ ID NO:131)
  - TM3-(37) YAIFVLYASAWNACFYICLFAGVMFLILSFLNCPFIVTLNI(SEQ ID NO:132)
  - TM3-(38) YAIFVLYFYICLFAGVCFLIASAWLSFLNCPFIVTLNI(SEQ ID NO:133)
  - 'IM3-(39) YAIFVLYASVDAVNMFTSAWLSFLNCPFIVTLNI(SEQ ID NO:134)
  - TM3-(40) YAIFSVDAVNMFTVLYASAWLSFLNCPFIVTLNI(SEQ ID NO:135)
- 20 TM3-(41) YAIFVLYASAWLSVDAVNMFTSFLNCPFIVTLNI(SEQ ID NO:136)
  - TM3-(42) YAIFVLYASAWLSFLNSVDAVNMFTPFIVTLNI(SEQ ID NO:137)
  - TM3-(43) YAIFVLYASAWLSFLNCPFIVSVDAVNMFTTLNI(SEQ ID NO:138)
  - TM3-(44) YAIFVLYASAWLSVDMFTSFLNCPFIVTLNI(SEQ ID NO:139)
  - TM3-(45) YAISVDAVNMFTFVLYASAWLSFLNCPFIVTLNI(SEQ ID NO:140)
- 25 TM3-(46) YAIFSLSVFSLLAIVLYASAWLSFLNCPFIVTLNI(SEQ ID NO:141)
  - TM3-(47) YAIFVLYASLSVFSLLAISAWLSFLNCPFIVTLNI(SEQ ID NO:142)
  - TM3-(48) YAIFVLYASAWLSLSVFSLLAISFLNCPFIVTLNI(SEQ ID NO:143)
  - TM3-(49) YAIFVLYASAWLSFLSLSVFSLLAINCPFIVTLNI(SEQ ID NO:144)
  - TM3-(50) YAIFVLYASAWLSFLNPFSLSVFSLLAIIVTLNI(SEQ ID NO:145)
- 30 TM3-(51) YAIFVLYATAWLTFLNCVTATIPFIVTLNI(SEQ ID NO:146)
  - TM3-(53) YAIFVLYATAWLSFLNVTLNICTTTIV (SEQ ID NO:148)
  - TM3-(54) YAIFVLYATAWLTFLNTATILNLMFIVTLNI(SEQ ID NO:149)

TM3-(52) YAIFVLYATAWLSFLNCTSSIVVTATIVTLNI(SEQ ID NO:147)

- TM3-(55) YAIFVLYATAWLSFLNMATILNLPFIVTLNI(SEQ ID NO:150)
- 35 TM3-(56) YAIFVLYATAWLTFLNSGILLLAPFIVTLNI(SEQ ID NO:151)
  - TM3-(57) YAIFVLYASAWLTFLNMTGILLLAPFIVTLNI(SEQ ID NO:152)
  - TM3-(58) YAIFVLYASAWLTFLNTELTVYTLTVCPFIVTLNI(SEQ ID NO:153)
  - TM3-(59) YAIFVLYASAWLTFLNMTELTVYTLTVPFIVTLNI(SEQ ID NO:154)
  - TM3-(60) YAIFVLYATAWLATELTVYTLTVTFLNCPFIVTLNI(SEQ ID NO:155)
- 40 TM3-(61) YAIFVLYASAWLATELSVYTLTVPFIVTLNI(SEQ ID NO:156)
  - TM3-(62) YAIFVLYATAWLSFLATELSVYASELSTTLTTVNMPFIVTLNI(SEQ ID NO:157)
  - TM3-(63) YAIFVLYATAWLSFLNGGEIALWTLCPFIVTLNI(SEQ ID NO:158)
  - TM3-(64) YAIFVLYASAWLTFLNGGEIALWTLIVTLNI(SEQ ID NO:159)
  - TM3-(65) YAIFVLYASAWLGGEIALWTLNCPFIVTLNI(SEQ ID NO:160)
- 45 TM3-(66) YAIFVLYAGGEIALWTLSFLNCPFIVTLNI(SEQ ID NO:161)

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- TM3-(67) YAIFVLYATAWLSFFFLLFGYLGNFLLNCPFIVTLNI(SEQ ID NO:162)
- TM3-(68) YAIFVLYATAWLFFFLLFGYLGNFLLPFIVTLNI(SEQ ID NO:163)
- TM3-(69) YAIFVLYATAWLTFLNTACFYVAITASLCFITEIALIPFIVTLNI(SEQ ID NO:164)
- TM3-(70) YAIFVLYATAWLTACFYVAITATLCFITEIALICPFIVTLNI(SEQ ID NO:165)
- 5 TM3-(71) YAIFVLYATACFYVAITATLCFITEIALISFLNCPFIVTLNI(SEQ ID NO:166)
  - TM3-(72) YAITACFYVAITASLCFITEIALIATAWLTFLNCPFIVTLNI(SEQ ID NO:167)
  - 'IM3 (73) YAIFVLYATACFYVAIITEIALITAWLTFLNCPFIVTLNI (SEQ ID NO:168)
  - TM3-(74) YAIFVLYASAWLTFLNACFYICLFAGVCFLIPFIVTLNI(SEQ ID NO:169)
  - TM3-(75) YAIFVLYASAWNACFYICLFAGVMFLILTFLNCPFIVTLNI(SEQ ID NO:170)
- 10 TM3-(76) YAIFVLYFYICLFAGVCFLIATAWLTFLNCPFIVTLNI(SEQ ID NO:171)
  - TM3-(77) YAIFVLYATVDAVNMFTTAWLTFLNCPFIVTLNI(SEQ ID NO:172)
  - TM3-(78) YAIFTVDAVNMFTVLYATAWLTFLNCPFIVTLNI(SEQ ID NO:173)
  - TM3-(79) YAIFVLYATAWLTVDAVNMFTSFLNCPFIVTLNI(SEQ ID NO:174)
  - TM3-(80) YAIFVLYATAWLSFLNTVDAVNMFTPFIVTLNI(SEQ ID NO:175)
- 15 TM3-(81) YAIFVLYASAWLTFLNCPFIVSVDAVNMFTTLNI(SEQ ID NO:176)
  - TM3-(82) YAIFVLYATAWLSVDMFTTFLNCPFIVTLNI(SEQ ID NO:177)
    - TM3-(83) YAISVDAVNMFTFVLYATAWLSFLNCPFIVTLNI(SEQ ID NO:178)
    - TM3-(84) YAIFVLYASLTVFSLLAISAWLTFLNCPFIVTLNI(SEQ ID NO:179)
    - TM3-(85) YAIFVLYASAWLTLSVFTLLAISFLNCPFIVTLNI(SEQ ID NO:180)
- 20 TM3-(86) YAIFVLYASAWLTFLSLSVFTLLAINCPFIVTLNI(SEQ ID NO:181)
  - TM3-(87) YAIFVLYASAWLTFLNPFSLSVFSLLAIIVTLNI(SEQ ID NO:182)
  - TM3-(88) YAIFVLYASAWLSFLNLGGVTASFTASVGPFIVTLNI(SEQ ID NO:183)
  - TM3-(89) YAIFVLYASAWLSFLNLGGVTASFTASVGVTLNI(SEQ ID NO:184)
  - TM3-(90) YAIFVLIGGVTASFTASVNYASAWLSFLNCPFIVTLNI(SEQ ID NO:185)
- 25 TM3-(91) YAIFVLYAIFFFLLFSAWLSFLNCPFIVTLNI(SEQ ID NO:186)
  - TM3-(92) YAIFVLYASAWLSFLNCPFIVTLNIIFFFLLFIVTLNI(SEQ ID NO:187)
  - TM3-(93) YAIFVLYASAWIFFFLLFLSFLNCPFIVTLNI(SEQ ID NO:188)
  - TM3-(94) YAIFVLYASAWLFFTVLASELSVYTLTVSFLNCPFIVTLNI(SEQ ID NO:189)
  - TM3-(95) YAIFVLYASAWLSFLFATLGGEIALCPFIVTLNI(SEQ ID NO:190)
- 30 TM3-(96) YAIFVLYAFATLGGEIALSAWLSFLNCPFIVTLNI (SEQ ID NO:191)
  - TM3-(97) YAIFFTVLASELSVYTLTVYASAWLSFLNCPFIVTLNI(SEQ ID NO:192)
  - TM3-(98) YAIFFPIAALFASIASAWLSFLNCPFIVTLNI(SEQ ID NO:193)
  - TM3-(99) YAIFVLYASAWLSFFPIAALFASIPFIVTLNI(SEQ ID NO:194)
  - TM3-(100) YAIFVLYASAWLSFLNCPFFPIAALFASILNI(SEQ ID NO:195)
- 35 TM3-(101) YAIFVLYASAWLSLDVLFSTASIMHLSFLNGGEIALWSLIVTLNI(SEQ ID NO:196)
  - TM3-(102) YAIFVLYASLDVLFSTASIMHLIALWSLNCPFIVTLNI(SEQ ID NO:197)
  - TM3-(103) YAIFVLYAGGEIALWSLSFLNSLDVLFSTASIMHLPFIVTLNI(SEQ ID NO:198)
  - TM3-(104) YAIFVLYASAWLSFFDVLFSTASIMHLFGYLGNFLLNCPFIVTLNI(SEQ ID NO:199)
  - TM3-(105) YAIFVLYASAWLFFFLLFGYLSLDVLFSTASIMHLGNFLLPFIVTLNI(SEQ ID NO:200)
- 40 TM3-(106) YAIFVLYASAWLSFLNTACFYVAITASLSLMHLFITEIALIPFIVTLNI (SEQ ID NO:201)
  - TM3-(107) YASLDVLFSTAIMHLSAWLTACFYVAITASLCFITEIALICPFIVTLNI(SEQ ID NO:202)
  - TM3-(108) YAIFVLYATACFYVAITASLSFLNCPFIVTLNISLDVLFSTASIMHL(SEQ ID NO:203)
  - TM3-(109) YAITACFYVAITASLCFITEIALIASAWLSFLNCPFIVTLNI(SEQ ID NO:204)
  - TM3-(110) YAIFVLYATACFYSTASILNLIMHLCAISLVAIITEIALISAWLSFLN(SEQ ID NO:205)
- 45 TM3-(111) YAIFVLYASAWLSFLNACFYICLFASILNLIMHLGVCFLIPFIVTLNI(SEQ ID NO:206)

- TM3-(112) YAIFVLYASAWNASILNLIMHLCFYICLFAGVMLILSFLNCPFIVTLNI(SEQ ID NO:207)
- TM3-(113) YAIFPFVQCVVSIFSLVLIAVVLYFYIAGVCFLIASAWLSFLNCPFIVTI(SEQ ID NO:208)
- TM3-(114) PFVOCVSITVSIFSLVLIAVYAIFVLYASVDAVNMFTSAWCPFIVTLNI(SEQ ID NO:209)
- TM3-(115) YAIFGDWSSVDAVNMFTVLYASAWLSFLNCPFIVTLNI(SEQ ID NO:210)
- 5 TM3-(116) YAIFVLYAGDWSSAWLSVDAVNMFTSFLNCPFIVTLNI(SEQ ID NO:211)
  - TM3-(117) YAIFVLYASAWLGDWSSFLNSVDAVNMFTPFIVTLNI(SEQ ID NO:212)
  - TM3-(118) YAIFVLYASAWLSFLNCPFIVGDWSSVDAVNMFTTLNI(SEQ ID NO:213)
  - TM3-(119) YAIFVLYASAWLGYLGSVDMFTSFLNCPFIVTGDWSLNI(SEQ ID NO:214)
  - TM3-(120) YAISVDAVNMFTFVLYAGYLGSAWLSFLNCPFIVTLNI(SEQ ID NO:215)
- 10 TM3-(121) YAIFSLSVFSLLAIVLYASAWLGYLGSFLNCPFIVTLNI (SEQ ID NO:216)
  - TM3-(122) YAIFVLYAGYLGAGNMDSLSVFSLLAISAWLSFLNCPFIVTLNI(SEQ ID NO:217)
  - TM3-(123) YAIFVLYASAWLSLSVFGNMSLLAISFLNCPFIVTLNI(SEQ ID NO:218)
  - TM3-(124) YAIFVLYASAWLSFLSLSVFGGSLLAINCPFIVTLNI(SEQ ID NO:219)
  - TM3-(125) YAIFVLYASAWLSFLNPFSLSVFGSLLAIIVTLNI(SEQ ID NO:220)
- 15 TM3-(126) YAIFVLYATAWLTFLSLANCVTATIPFIVTLNI(SEO ID NO:221)
  - TM3-(127) YAIFVLYATAWLSFLNCTSLASSIVVTATIVTLNI(SEQ ID NO:222;
  - TM3-(128) YAIFVLYATAWLSFLNVTLNISLACTTTIV (SEQ ID NO:223)
  - TM3-(129) YAIFVLYATAWLTFLNTATILSLANLMFIVTLNI(SEQ ID NO:224)
  - TM3-(130) YAIFVLYATAWLSFLNMATILNLPFSVDAVIVTLNI(SEQ ID NO:225)
- Recently discovered G-proteins also can be used according 20 to the presently claimed invention to provide GPR polypeptides of the present invention, based on the teaching and guidance presented herein. Exampled of such GPR polypeptides of the present invention may include, as non-limiting examples, GPR polypeptides corresponding 25 to transmembrane domain III, e.g., as follows:
  - TM3-(131) ISTMYTVTGRWTLGQVVCDFWLSSDITCCTASILHLCVIAL (SEQ ID NO:226)
  - TM3-(132) ILYGYRWPLPSKLCAVWIYLDVLFSTASIMHLCAISL (SEQ ID NO:227)
  - TM3-(133) IIYI VMDRWKLGYFLCEVWLSVDMTCCTCSILHLCVIAL (SEQ ID NO:228)
  - TM3-(134) IADKTVRVAMGAENDLGYNFRSDDVCGHCWQWYCSL (SEQ ID NO:229)
- 30 TM3-(135) ILNYWPFGLALCHFVNYSQAVSVLVSAYTLVAISI (SEQ ID NO:230)
  - TM3-(136) ILGRWEFGIHLCKLWLTCDVLCCTSSILNLCAIALD (SEQ ID NO:231)
  - TM3-(137) IMASVMHRHCLPLIGICLSSERHCLVSIFVELGAL (SEQ ID NO:232)

Further non-limiting examples of consensus GPR polypeptides for transmembrane domain III of several or many, such as 1-500, or 35 any range or value therein, more recently discovered G-protein receptors are as follows:

- TM3-(138) YAIFVLYASAWLSFLNCPFISILHLCVIALVTLNI(SEQ ID NO:233)
- TM3-(139) YAIFVLYATAWLSFLNCPFISILNLCAIALDVTLNI(SEQ ID NO:234)

- TM3-(140) YAIFVLYATAWLTFLNCPFISIFVELGALVTLNI(SEQ ID NO:235)
- TM3-(141) YAIFVLYASAWLTFLNCPFISIFVELSIMHLCAISLGALVTLNI(SEQ ID NO:236)
- TM3-(142) WAIFVLYAILGRWEFGIHLCKLWLTSAWLSIMHLCAISLSFLNCPFIVTLNI(SEQ ID NO:237)
- TM3-(143) WAIFVLYAILGRWEFGIHLCKLWLTTAWLSIMHLCAISLSFLNCPFIVTLNI(SEQ ID NO:238)
- 5 TM3-(144) WAIFVLYATAWLTFLNCPFSIMHLCAISLIVTLNI(SEQ ID NO:239)
  - TM3-(145) WAIFVLYASAWLTFLNCPFISIMHLCAISLVTLNI(SEQ ID NO:240)
  - TM3-(146) YAVFVLYASAWLSFLNMSIMHLCAISLPFIVTLNI(SEQ ID NO:241)
  - TM3-(147) YAVFVLYATAWLSFLNMPFSILNLCAIALDIVTLNI(SEQ ID NO:242)
  - TM3-(148) YAVFVLYATAWLSILNLCAIALDTFLNMPFIVTLNI(SEQ ID NO:243)
- 10 TM3-(149) YAVFVLYASILNLCAIALDSAWLTFLNMPFIVTLNI(SEQ ID NO:244)
  - TM3-(150) YAIFVLYASAWLSFLNCVTASIPFCLVSIFVELGALIVTLNI(SEQ ID NO:245)
  - TM3-(151) YAIFVLYASAWLSFLNCLVSIFVELGALIVVTASIVTLNI(SEQ ID NO:246)
  - TM3-(152) YAIFVLYASAWLSFLNVTLNCLVSIFVELGALII(SEQ ID NO:247)
  - TM3-(153) YAIFVLYASAWLSFLNTASILNLMFICLVSIFVELGALVTLNI(SEQ ID NO:248)
- 15 TM3-(154) YAIFVLYASAWLSFLNMASILNLPFCLVSIFVELGALVTLNI(SEQ ID NO:249)
  - TM3-(155) YAIFVLYASAWLSFLNILGRWEFGIHLCKLWLTCDVLCCTSSGILLLAPFIVTLNI(SEQ ID NO:250)
  - TM3-(156) YAIFVLYASAWLSFLNMILGRWEFGIHLCKLWLTCDVLCCTSSGILLLAPFIVTLNI(SEQ ID NO:251)
  - TM3-(157) YAIFVLYASAWLILGRWEFGIHLCKLWLTCDVLCCTSSFLNSELSVYTLTVCPFIVTLNI(SEQ ID
  - NO:252)
- 20 TM3-(158) YAIFVLYAILGRWEFGIHLCKLWLTCDVLCCTSSAWLSFLNMSELSVYTLTVPFIVTLNI(SEQ ID NO:253)
  - TM3-(159) YAIFVLYASAWLASRWPLPLSVYTLTVSFLNCPFIVTLNI(SEQ ID NO:254)
  - TM3-(160) YAIFVLYASAWLASELILYYWRWPLPCLHDLVWLCTCSILHLCVIALSV/TLTVPFIVTLNI(SEQ ID NO:255)
- 25 TM3-(161) YAIFVLYASAWLSFLASELSVYASELSSTLHDLVWLWLDVFCVIALTTVNMPFIVTLNI(SEQ ID
  - NO:256)

    TM3-(162) YAIFVLYASAWLSFLNGGEIALWSLCPFIILYYWRWPLPCLHDLVSILHLCVIALVTLNI(SEQ ID
    NO:257)
- TM3-(163) YVWLWLDVFCCTCSILHLCVIALFVLYASAWLSFLNGGEIALWSLIVTLNI(SEQ ID NO:258)
- 30 TM3-(164) YAIFVLYASAWLAIILYYWRWPLPCLHDLGGEIALWSLNCPFIVTLNI(SEQ ID NO:259)

Non-limiting examples of consensus GPR polypeptides for domain V across several or many, such as 1-500, or any range or value therein, G-protein receptors are as follows:

- TM5-(1) CDVFVFVDIMLCTASIFNLCAISVG(SEQ ID NO:260)
- 35 TM5-(2) YAIFVLYDIMLCTASIFNLCAISVG(SEQ ID NO:261)
  - TM5-(3) DYAIFVFVDIMLMTASIFNLMAISVG(SEQ ID NO:262)
  - TM5-(4) DYAIFVFVDIMLHTTASTIFNLMATITVG(SEQ ID NO:263)
  - TM5-(5) CDVAVVYSSDIMLFYVCTASIFSSNLCAISSVG(SEQ ID NO:264)
  - TM5-(6) FLFCSLGSFYIPIAVILVDIMLCTASIFNLCAISVG(SEQ ID NO:265)
- 40 TM5-(7) YAIFVLYDFLFCSLGSFYIPIAVILIMLCTASIFNLCAISVG(SEQ ID NO:266)
  - TM5-(8) DYAIFVFVDIMLMTASIFLFCSLGSFYIPIAVILISVG(SEQ ID NO:267)
  - TM5-(9) DYAIFVFVDIMLHTTASTIFNLMAFLFCSLGSFYIPIAVILTITVG(SEQ ID NO:268)

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TM5-(10) CDVAVVYSSDIMLFYVCTASIFSSNLFLFCSLGSFYCAISSVG(SEQ ID NO:269) TM5-(11) CDVFVFVDIMLCTASIFNWYILSSIGSFFAPCLILLVYLLCAISVG(SEQ ID NO:270) TM5-(12) YAIFVLYDIMLCTASIFNLCAIWYILSSIGSFFAPCLILLVYLSVG(SEQ ID NO:271) TM5-(13) DYAIFVFVDIWYILSSIGSFFAPCLILLVYLASIFNLMAISVG(SEQ ID NO:272) 5 TM5-(14) DYAIWYILSSIGSFFAPCLILLVYLIMLHTTASTIFNLMATITVG(SEQ ID NO:273) TM5-(15) CDVAVVYSSDIMLFYVCWYILSSIGSFFAPCLILLVYLSSNLCAISSVG(SEQ ID NO:274) TM5-(16) CDVFVFVDIMLCTASIFWYVISSSIGSFFAPCLINHLVYNLCAISVG(SEQ ID NO:275) TM5-(17) YAIFVLYDIMLCTASIFNLCAIWYVISSSIGSFFAPCLINHLVYSVG(SEQ ID NO:276) TM5-(18) DYAIFVFVWYVISSSIGSFFAPCLINHLVYDIMLMTASIFNLMAISVG (SEQ ID NO:277) 10 TM5-(19) DYAIFVFVDIMLHTTASTIFWYVISSSIGSFFAPCLINHLVYTVG(SEQ ID NO:278) TM5-(20) CDVAVVYSSDIMLFYVCTASIFSWYVISIGSFFAINHLVYNLCAISSVG(SEQ ID NO:279) TM5-(21) CDVFVFVDIMLCTASIFNLCAITYAISSSVISFYIPVAILVTYT(SEQ ID NO:280) TM5-(22) YAIFVLYDIMLCTATYAISSSVISFYIPVAILVTYTSIFNLCAISVG(SEQ ID NO:281) TM5-(23) DYAIFVFVDIMLMTATYAISSSVISFYIPVAILVTYTISVG(SEQ ID NO:282) 15 TM5-(24) TYAISSSVISFYIPVATDYAIFVFVDIMLHTTASTIFNLMATITVG(SEQ ID NO:283) TM5-(25) CDVAVVYSSDIMLFYVCTATYAISSSVISFYIPVAILVTYTSSVG(SEQ ID NO:284) TM5-(26) CDVFVFVDFVIYSSVVSFYLPFGVTVLVYACTASIFNLCAISVG(SEQ ID NO:285) TM5-(27) YAIFVLYDFVIYSSVVSFYLPFGVTVLVYASIFNLCAISVG(SEQ ID NO:286) TM5-(28) DYAIFVFVDFVIYSSVVSFYLPFGVTVLVYATASIFNLMAISVG(SEQ ID NO:287) 20 TM5-(29) DYAIFVFVDFVIYSSVVSFYLPFGVTVLVYAHTTASTIFNLMATITVG(SEQ ID NO:288) TM5-(30) CDVAVVYSSDFVIYSSVVSFYLPFGVTVYVCTASIFSSNLCAISSVG(SEQ ID NO:289) TM5-(31) CDVFVFVDIMLCTASYTIYSTCGAFYIPSVLLIILYGNLCAISVG(SEQ ID NO:290) TM5-(32) YAIFVLYDIMLCTASYTIYSTCGAFYIPSVLLIILYGNLCAISVG(SEQ ID NO:291) TM5-(33) DYAIFVFVDIMLMTASYTIYSTCGAFYIPSVLLIILYGNLMAISVG(SEQ ID NO:292) 25 TM5-(34) DYAIFVFVDIMLHTTASYTIYSTCGAFYIPSVLLIILYGMATITVG (SEQ ID NO:293) TM5-(35) CDVAVVYSSDIMSYTIYSTCGAFYIPSVLLIILYGIFSSNLCAISSVG(SEQ ID NO:294) TM5-(36) CDVFVFFVLIGSFVAVDIMLCTASIFNLCAISVG(SEQ ID NO:295) TM5-(37) YAIFVLYFVLIGSFVADIMLCTASIFNLCAISVG(SEQ ID NO:296) TM5-(38) DYAIFVFVFVLIGSFVADIMLMTASIFNLMAISVG(SEQ ID NO:297) 30 TM5-(39) DYAIFVFVFVLIGSFVADIMLHTTASTIFNLMATITVG(SEQ ID NO:298) TM5-(40) CDVAVVYSSFVLIGSFVADIMLFYVCTASIFSSNLCAISSVG(SEQ ID NO:299) TM5-(41) CDVFVFVDIMLCFFIPTLIMVITYFNLCAISVG(SEQ ID NO:300) TM5-(42) YAIFVLYDIMLCFFIPTLIMVITYFFNLCAISVG(SEQ ID NO:301) TM5-(43) DYAIFVFVDIMLMFFIPTLIMVITYFNLMAISVG(SEQ ID NO:302) 35 TM5-(44) DYAIFVFVDIMLHTFFIPTLIMVITYFNLMATITVG(SEQ ID NO:303) TM5-(45) CDVAVVYSSDIMLFYVCFFIPTLIMVITYFSSNLCAISSVG(SEQ ID NO:304) TM5-(46) CDVVYGLVDGLVTFYLPLLIMCITYYDIMLCTASIFNLCAISVG(SEQ ID NO:305) TM5-(47) YAIVYGLVDGLVTFYLPLLIMCITYYDIMLCTASIFNLCAISVG(SEQ ID NO:306) TM5-(48) DYAIVYGLVDGLVTFYLPLLIMCITYYDIMLMTASIFNLMAISVG(SEQ ID NO:307) 40 TM5-(49) DYAIVYGLVDGLVTFYLPLLIMCISSDIMLHTTASTIFNLMATITVG(SEQ ID NO:308) TM5-(50) CDVVYDGLVTFYLPLLIMCITYYDIMLFYVCTASIFSSNLCAISSVG(SEQ ID NO:309) TM5-(51) CDVFVFVDIMLLVIFLGLVIVIPFVLIIVSYASIFNLCAISVG(SEQ ID NO:310) TM5-(52) YAIFVLYDIMLLVIFLGLVIVIPFVLIIVSYAIFNLCAISVG(SEQ ID NO:311) TM5-(53) DYAIFVFVDIMLMLVIFLGLVIVIPFVLIIVSYAIFNLMAISVG(SEQ ID NO:312) 45 TM5-(54) DYAIFVFVDIMLHTLVIFLGLVIVIPFVLIIVSYAIFNIMATITVG(SEQ ID NO:313)

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	TM5-(55) CDVAVVYSSI	IMLFLVIFLGLVIVI	PFVLIIVSYAIFS	SNLCAISSVG (SE)	Q ID NO:314)	
	TM5-(56) CDVFVFVDIM	ILCTALMIYILGGLII	IIPFLLIVMSYVS	IFNLCAISVG(SE	Q ID NO:315)	
	TM5-(57) YAIFVLYDIM	ILCTALMIYILGGLII	IIPFLLIVMSYVS	IFNLCAISVG (SE	Q ID NO:316)	
	TM5-(58) DYAIFVFVDI	MLMTASIFNLMIYIL	GGLIIIIPFLLIV	MSYVLMAISVG(SI	EQ ID NO:317)	
5	TM5-(59) DYAIFVFVDI	MLHTTASTILMIYIL	GGLIIIIPFLLIV	MSYVITVG(SEQ	ID NO:318)	
	TM5-(60) CDVAVVYSSD	IMLFYVCTAYILGGL	IPFLLIVMTYVSI	FTNLCAISSVG (SI	EQ ID NO:319)	
	TM5-(61) CDVFVFVDIM	ILCTASIFNLLMIHIM	EVIIIVIPFVLIV	ISYACAISVG(SE	Q ID NO:320)	
	TM5-(62) YAIFVLYDIM	ILCTASIFNLLMIHIM	<b>EVI</b> IIVIPFVLIV	ISYACAISVG(SE	Q ID NO:321)	
	TM5-(63) DYAIFVFVDI	MLMTASIFLMIHIME	VIIIVIPFVLIVI	SYAISVG(SEQ II	NO:322)	
10	TM5-(64) DYAIFVFVDI	MLHTTASTILMIHIM	<b>EV</b> IIIVIPFVLIV	ISYAITVG(SEQ	ID NO:323)	
	TM5-(65) CDVAVVYSSD	IMLFYVCTASIFLMI	HIMEVIIIVIPFV	LIVISYAAISSVG	(SEQ ID NO:324	1)
	Non-li	miting exampl	es of longe	r concensus	GPP polymer	tides
			_			
	for domain V acr				or any val	ue or
	range therein, G	}-protein rece	eptors are	as follows:		
15	T M	1	-	(	1	)
	TM1NWPALSIVVIIINTIG	GNILVIMAVSIYTSL	DVMLCTASILNLL	ISLFVLIGSFVAF	FIPLTIMVITYFLF	NVFFVW
	IGYVCSSSLGINPVIIYTI	F(SEQ ID NO:325	)			
	T M	1	-	(	2	)
	NWPALSIVVIIINTIGGNI	LVIMAVTIYTTLDVM	LCTATILNLLISL	<b>FVLIGTFVAFFI</b> PI	LTIMVITYFLFNVF	FVWIGY
20	VCTTTLGINPVIIYTLF (S	EQ ID NO:326)				
	T M	1	-	(	3	)
	NWPALTIVVIIINTIGGNI		LCTATILNLLITL	FVLIGTFVAFFIP	LTIMVITYFLFNVF	FVWIGY
	VCSTSLGINPVIIYTLF (S	-				
۰-	T M	1	- 	(	5	)
25	NWPALTIVVIIINTIGGNI		LCTATILNLLITL	FVLIGTFVAFF1P1	CTIMVITYFLFNVF	FVWIGY
	VCTLGINPVIIYTLF (SEC	•		,		,
	T M	1	-	( 	6	)
	NWKNWSALLTTVVIILTIA		LCTASILNLLISL	FVLIGSFVAFFIP	STIMVITYFLENVE	FVWIGY
30	VCSSSLGINPVIIYTLF(S	1 no:329/		1	7	,
30	ITITVVLAVLILITVAGNV		- את מייי אפדו את די די פ	l Tem Teermert	·	) 
	YVCSSSLGINPVIIYTLF(		MUCIASIMULIS	TE ATTORE AME E T	STITMATITETEMA	/FFVWIG
	T M	1 (SEQ 10 NO.330)	_	1	8	,
	TLTLVCIACLUSLTVFGNV	_	ASTINT.I.TSI.FVI.	, TGGEWAFFTDT.TT	_	, MENTON
35	SSLGINPVIIYTLF (SEQ		ADIDAL VI	1001 VALT 11 2111	2011111 DrHVP1 VV	11G1 VC5
-	T M	1	_	(	9	١
	TAAIAAAITFLILFTIFGN		VMI.CTASTI.NI.I.T	SI.FVI.TGSFVAFF	-	, TVFFFVMT
	GYVCSSSLGINPVIIYTLE					
	T M	1	- (	1	0	)
40	AISVGLVLGAFILFAIVGN	_	VVIIINTIGGNIL	_	_	LFVLIGS
	FVAFFIPLTIMVITYFLFN					

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	T	M	1	•		(	1	1	)
	AALAGALI	LALAVLATV	GGNLLVIVAIA	SLDVMLCTASI:	LNLLISLE	VLIGSFVA	FFIPLTIMVI	TYFLFNVFFVW	IGYVC
	SSSLGINE	VIIYTLF (	SEQ ID NO:3	34)					
	T	M	1	-		(	1	2	)
5	TAGDCLIN	ILIVLLIVA	GNVLVIVAISL	DVMLCTASILN	LLISLFVI	LIGSFVAFF	IPLTIMVITY	FLFNVFFVWIG	YVCSS
	SLGINPVI	IYTLF (SE	Q ID NO:335	)					
	Т	M	1	_		(	1	3	)
	VITIAVVI	'AVVSL <b>MT</b> 'I	VGNVLVMISFS	IYTSLDVMLCT.	ASILNLL]	SLFVLIGS	FVAFFIPLTI	MVITYFLFNVF	FVWIG
	YVCSSSLO	SINPVIIYI	LF (SEQ ID N	iO:336)					
10	Т	M	1	-		(	1	4	)
	MVFIATV	RGSLSLVTV	VGNILVMLSIS	IYTSLDVMLCT	ASILNLL	SLFVLIGS	FVAFFIPLTI	MVITYFLFNVF	FVWIG
	YVCSSSLO	TYLIVANIE	LF (SEQ ID N	IO:337)					
	T	M	1	-		(	1	5	)
	WFIAFLTO	SILALVTII	GNILVIVSFSI	YTSLDVMLCTA	SILNLLIS	SLFVLIGSF	VAFFIPLTI <b>M</b>	VI <b>T</b> YFLF <b>N</b> VFF	VWIGY
15	VCSSSLG	ITYIIV9MI	F(SEQ ID NO	):338)					
		Non-	-limiting	examples o	of lone	er cons	ensus GPI	R polypept	ides
	for do		_	veral or m					
								. any vara	01
	range	therein	, G-prote	in recepto	ors are	as loi	TOWS:		
	T	M	3	-	(	1	6	5	)
20	NWPALSI	VVIIIVT	GNILVIMAFF?	ACFVLVLTQSSI	FSLLAIA	INLLISLFV	LIGSFVAFFI	PLTIMVITYFI	PNVFF
	VWIGYVC	SSSLGI <b>N</b> P\	/IIYTLF (SEQ	ID NO:339)					
	T	M	3	-	(	1	6	6	)
	NWPALSI	VVIIINTI	GNILVIMAFF!	ACFVLVLTQSSI	FSLLAIA	IFVLIGSFV	AFFIPLTIMV	TTYFLFNVFFV	WIGYV
	CSSSLGI	NPVIIYTL	F(SEQ ID NO	: 340)					
25	T	M	3	-	(	1	6	7	)
				VACPVLILTQSS	IIALLAI.	avsfvaffi	PLTIMVITYF	LFNVFFVWIGY	rvcsss
	LGINPVI	IYTLF (SE	Q ID NO:341)	•					
	T	M	3	-	(	1	6	8	)
	NWPALSI	VVIIINTI	GGNILVIMAVL	WLALDYVASNAS	VLNLLLI	SFFFIPLTI	MVITYFLFN	/FFVWIGYVCSS	SSLGIN
30	PVIIYTL	F(SEQ ID	NO:342)				_	_	
	_	M	-	-	(	1	6	9	)
				LIMMVZAMSVVY	LIISSFVA	FFIPLTIM	/ITYFLFNVF	/VWIGYVCSSSI	LGINPV
	IIYTLF (	SEQ ID N	D:343)				_	_	
	T	M	3	-	(	1	7 	0	)
35				WIAIDYVASNAS	SVLNLLVI	SFGSFVAFI	TPLTIMVITY	(FLFNVFFVWIC	3YVCSS
	SLGINPV	TIYTLF (S	EQ ID NO:34	4)			_		
	T	M	3	-	(	1	7	1	)
				FPFLQKSSVGI	TVLNLCAL	SGSFVAFF	[PLTIMVITY]	FLFNVFFVWIG	YVCSSS
	LGINPVI	IYTLF (SE	Q ID NO:345	)				_	
40	T	M	3	-	(	1	7	2	)
	NWPALSI	VVIIINTI	GGNILVI <b>M</b> AVC	ITYLQYLGINA	SSCSITAF	TIIGSFVA	FFIPLTIMVI	TYFLFNVFFVW	IGYVCS
	SSIGINE	VTTVTTF (	SEC ID NO:3	46)					

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T M 3 - ( 1 7 3 )

NWPALSIVVIIINTIGGNILVIMAVFHNFFPIAALFASIYSMTAVAGSFVAFFIPLTIMVITYFLFNVFFVWIGYVCSSS

LGINPVIIYTLF(SEQ ID NO:347)

T M 3 - ( 1 7 4 )

5 NWPALSIVVIIINTIGGNILVIMAVIASASVSFNLYASVFLLTCLSIGSFVAFFIPLTIMVITYFLFNVFFVWIGYVCSS

SLGINPVIIYTLF(SEQ ID NO:348)

As another non-limiting, illustrative example of a GPR polypeptide consensus sequences across each individual or different transmembrane domains of 5-HT receptors may be made, such as for 5-10 HT, as the following:

5HT consensus (4) KNASALLSVIIINSIGGNVVTAVS (SEQ ID NO:349);

5HT consensus(5) YFLMSLAVTDLVVSFVMPVSAL (SEQ ID NO:350);

5HT consensus(6) AITKIAITWAISGVSVPFIPVWG (SEQ ID NO:351); and

15 5HT consensus(7) LGIIFGTFIIIWLPFFITNLVSPI (SEQ ID NO:352);

Wherein variations and substitutions of amino acids may be made as described herein.

Alternatively, 5-HT consensus sequences may be provided as consensus peptides of the present invention as consensus 20 peptides for individual transmembrane domains, such as 5-HT domains III, V and VII, e.g., as follows:

5-HT consensus (8): IWISLDVLFSTASSIMHLCAISL (SEQ ID NO:353)

5-HT consensus (9): GYTIYSTLVTFYIPSVIMVITYG (SEQ ID NO:354)

5-HT consensus (10): LLNFFNWIGYLNSLINPVIYTLF (SEQ ID NO:355)

This invention is also directed to an antibody which binds an epitope specific for a GPR polypeptide of the present invention and the use of such an antibody to detect the presence of, or measure the quantity or concentration of, the GPR protein in a cell, a cell or tissue extract, a biological fluid, an extract thereof, a solution, or sample, in vitro, in situ, or in vivo.

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The term "antibody" is meant to include polyclonal antibodies, monoclonal antibodies (mAbs), chimeric antibodies, anti-idiotypic (anti-Id) antibodies to antibodies specific for GPR polypeptide of the present invention, as well as fragments, consensus polypeptides or chemical derivatives thereof.

Polyclonal antibodies are heterogeneous populations of antibody molecules derived from the sera of animals immunized with an antigen.

A monoclonal antibody contains a substantially homogeneous 10 population of antibodies specific to antigens, which population contains substantially similar epitope binding sites. MAbs may be obtained by methods known to those skilled in the art. example Kohler and Milstein, Nature 256:495-497 (1975); U.S. Patent No. 4,376,110; Ausubel et al, eds., Current Protocols in Molecular 15 Biology, Wiley Interscience, N.Y., (1987, 1992); and Harlow and Lane Antibodies: A Laboratory Manual Cold Spring Harbor Laboratory (1988), the contents of which references are incoporated entirely herein by reference. Such antibodies may be of any immunoglobulin class including IgG, IgM, IgE, IgA, GILD and any subclass thereof. 20 hybridoma producing a mAb of the present invention may be cultivated in vitro, in situ or in vivo. Production of high titers of mAbs in vivo or in situ makes this the presently preferred method of production.

Chimeric antibodies are molecules different portions of
which are derived from different animal species, such as those having
variable region derived from a murine mAb and a human immunoglobulin
constant region, which are primarily used to reduce immunogenicity
in application and to increase yields in production, for example,
where murine mAbs have higher yields from hybridomas but higher
immunogenicity in humans, such that human/murine chimeric mAbs are
used. Chimeric antibodies and methods for their production are known
in the art (Cabilly et al, Proc. Natl. Acad. Sci. USA 81:3273-3277
(1984); Morrison et al., Proc. Natl. Acad. Sci. USA 81:6851-6855
(1984); Boulianne et al., Nature 312:643-646 (1984); Cabilly et al.,
European Patent Application 125023 (published November 14, 1984);
Neuberger et al., Nature 314:268-270 (1985); Taniguchi et al.,
European Patent Application 171496 (published February 19, 1985);

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Morrison et al., European Patent Application 173494 (published March 5, 1986); Neuberger et al., PCT Application WO 86/01533, (published March 13, 1986); Kudo et al., European Patent Application 184187 (published June 11, 1986); Morrison et al., European Patent 5 Application 173494 (published March 5, 1986); Sahagan et al., J. Immunol. 137:1066-1074 (1986); Robinson et al., International Patent Publication No.PCT/US86/02269 (published 7 May 1987); Liu et al., Proc. Natl. Acad. Sci. USA 84:3439-3443 (1987); Sun et al., Proc. Natl. Acad. Sci. USA 84:214-218 (1987); Better et al., Science 10 240:1041- 1043 (1988); and Harlow and Lane Antibodies: A Laboratory Manual Cold Spring Harbor Laboratory (1988)). These references are incorporated entirely herein by reference.

An anti-idiotypic (anti-Id) antibody is an antibody which recognizes unique determinants generally associated with the antigen-15 binding site of an antibody. An Id antibody can be prepared by immunizing an animal of the same species and genetic type (e.g., mouse strain) as the source of the mAb with the mAb to which an anti-Id is being prepared. The immunized animal will recognize and respond to the idiotypic determinants of the immunizing antibody by 20 producing an antibody to these idiotypic determinants (the anti-Id antibody). See, for example, U.S. patent No. 4,699,880, which is herein entirely incorporated by reference.

The anti-Id antibody may also be used as an "immunogen" to induce an immune response in yet another animal, producing a so-25 called anti-anti-Id antibody. The anti-anti-Id may be epitopically identical to the original mAb which induced the anti-Id. Thus, by using antibodies to the idiotypic determinants of a mAb, it is possible to identify other clones expressing antibodies of identical specificity.

Accordingly, mAbs generated against a GPR polypeptide of the present invention may be used to induce anti-Id antibodies in suitable animals, such as BALB/c mice. Spleen cells from such immunized mice are used to produce anti-Id hybridomas secreting anti-Id mAbs. Further, the anti-Id mAbs can be coupled to a immunogenic 35 carrier such as keyhole limpet hemocyanin (KLH) or cationized bovine serum albumin and used to immunize additional BALB/c mice. Sera from these mice will contain anti-anti-Id antibodies that have the binding

properties of the original mAb specific for a GPR polypeptide epitope.

The anti-Id mAbs thus have their own idiotypic epitopes, or "idiotopes" structurally similar to the epitope being evaluated.

The term "antibody" is also meant to include both intact molecules as well as fragments thereof, such as, for example, Fab and F(ab')<sub>2</sub>, which are capable of binding antigen. Fab and F(ab')<sub>2</sub> fragments lack the Fc fragment of intact antibody, clear more rapidly from the circulation, and may have less non-specific tissue binding than an intact antibody (Wahl et al., J. Nucl. Med. 24:316-325 (1983)).

It will be appreciated that Fab and  $F(ab')_2$  and other fragments of the antibodies useful in the present invention may be used for the detection and quantitation of a GPR polypeptide according to the methods disclosed herein for intact antibody molecules. Such fragments are typically produced by proteolytic cleavage, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce  $F(ab')_2$  fragments).

An antibody is said to be "capable of binding" a molecule

20 if it is capable of specifically reacting with the molecule to
thereby bind the molecule to the antibody. The term "epitope" is
meant to refer to that portion of any molecule capable of being bound
by an antibody which can also be recognized by that antibody.

Epitopes or "antigenic determinants" usually consist of chemically

25 active surface groupings of molecules such as amino acids. lipids or
sugar side chains and have specific three dimensional structural
characteristics as well as specific charge characteristics.

An "antigen" is a molecule or a portion of a molecule capable of being bound by an antibody which is additionally capable of inducing an animal to produce antibody capable of binding to an epitope of that antigen. An antigen may have one, or more than one epitope. The specific reaction referred to above is meant to indicate that the antigen will react, in a highly selective manner, with its corresponding antibody and not with the multitude of other antibodies which may be evoked by other antigens.

The antibodies, or fragments of antibodies, useful in the present invention may be used to quantitatively or qualitatively

detect a GPR polypeptide in a sample or to detect presence of cells which express a GPR polypeptide of the present invention. This can be accomplished by immunofluorescence techniques employing a fluorescently labeled antibody (see below) coupled with light microscopic, flow cytometric, or fluorometric detection.

The antibodies (of fragments thereof) useful in the present invention may be employed histologically, as in immunofluorescence or immunoelectron microscopy, for in situ detection of a GPR polypeptide of the present invention. In situ detection may be accomplished by removing a histological specimen from a patient, and providing the a labeled antibody of the present invention to such a specimen. The antibody (or fragment) is preferably provided by applying or by overlaying the labeled antibody (or fragment) to a biological sample. Through the use of such a procedure, it is possible to determine not only the presence of a GPR polypeptide but also its distribution on the examined tissue. Using the present invention, those of ordinary skill will readily perceive that any of wide variety of histological methods (such as staining procedures) can be modified in order to achieve such in situ detection.

Such assays for a GPR polypeptide of the present invention typically comprise incubating a biological sample, such as a biological fluid, a tissue extract, freshly harvested cells such as lymphocytes or leukocytes, or cells which have been incubated in tissue culture, in the presence of a detectably labeled antibody capable of identifying a GPR polypeptide, and detecting the antibody by any of a number of techniques well-known in the art. See, e.g., Harlow and Lane, supra; Ausubel et al, supra; and Sambrook et al, supra.

The biological sample may be treated with a solid phase support or carrier, such as nitrocellulose, or other solid support or carrier which is capable of immobilizing cells, cell particles or soluble proteins. The support or carrier may then be washed with suitable buffers, followed by treatment with a detectably labeled GPR polypeptide-specific antibody. The solid phase support or carrier may then be washed with the buffer a second time to remove unbound antibody. The amount of bound label on said solid support or carrier

may then be detected by known method steps, see, e.g., Harlow, <u>supra;</u>
Ausubel, <u>supra;</u> or Sambrook, <u>supra</u>.

By "solid phase support", "solid phase carrier", "solid support", "solid carrier", "support" or "carrier" is intended any 5 support or carrier capable of binding antigen or antibodies. Wellsupports or carriers, include glass, polystyrene, polypropylene, polyethylene, dextran, nylon amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite. nature of the carrier can be either soluble to some extent or 10 insoluble for the purposes of the present invention. The support material may have virtually any possible structural configuration so long as the coupled molecule is capable of binding to an antigen or antibody. Thus, the support or carrrier configuration may be spherical, as in a bead, or cylindrical, as in the inside surface of 15 a test tube, or the external surface of a rod. Alternatively, the surface may be flat such as a sheet, polymer test strip, etc. Preferred supports or carriers include polystyrene beads. Those skilled in the art will know many other suitable carriers for binding antibody or antigen, or will be able to ascertain the same by use of 20 routine experimentation.

The binding activity of a given lot of anti-GPR polypeptide antibody may be determined according to well known method steps. Those skilled in the art will be able to determine operative and optimal assay conditions for each determination by employing routine experimentation. See, e.g., Harlow, <u>supra</u>.

Other such steps as washing, stirring, shaking, filtering and the like may be added to the assays as is customary or necessary for the particular situation.

One of the ways in which a GPR polypeptide-specific antibody, anti-idiotype antibody or fragment thereof, can be detectably labeled is by linking the same to an enzyme and use in an enzyme immunoassay (EIA). This enzyme, in turn, when later exposed to an appropriate substrate, will react with the substrate in such a manner as to produce a chemical moiety which can be detected, for example, by spectrophotometric, fluorometric or by visual means. Enzymes which can be used detectably label the antibody include, but are not limited to, malate dehydrogenase, staphylococcal nuclease,

delta-5-steroid isomerase, yeast alcohol dehydrogenase, alphaglycerophosphate dehydrogenase, triose phosphate isomerase,
horseradish peroxidase, alkaline phosphatase, asparaginase, glucose
oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose6- phosphate dehydrogenase, glucoamylase and acetylcholinesterase.
The detection can be accomplished by colorimetric methods which
employ a chromogenic substrate for the enzyme. Detection may also
be accomplished by visual comparison of the extent of enzymatic
reaction of a substrate in comparison with similarly prepared
standards. See, Harlow, supra, Ausubel, supra.

Detection may be accomplished using any of a variety of other immunoassays. For example, by radioactivity labeling the antibodies or antibody fragments, it is possible to detect R-PTPase through the use of a radioimmunoassay (RIA). A good description of RIA maybe found in Laboratory Techniques and Biochemistry in Molecular Biology, by Work et al., North Holland Publishing Company, NY (1978) with particular reference to the chapter entitled "An Introduction to Radioimmune Assay and Related Techniques" by Chard, incorporated entirely by reference herein. The radioactive isotope can be detected by such means as the use of a γ-counter, a scintillation counter or by autoradiography.

It is also possible to label an anti-GPR polypeptide antibody, anti-idiotype antibody or fragment thereof, with a fluorescent compound. When the fluorescently labeled antibody is exposed to light of the proper wave length, its presence can be then be detected due to fluorescence. Among the most commonly used fluorescent labelling compounds are fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, o-phthaldehyde and fluorescamine, commercially available, e.g., from Molecular Probes, Inc. (Eugene, Ore.).

The antibody can also be detectably labeled using fluorescence emitting metals such as <sup>152</sup>EU, or others of the lanthanide series. These metals can be attached to the antibody using such metal chelating groups as diethylenetriamine pentaacetic acid (EDTA).

The antibody also can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the

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chemiluminescent-tagged antibody is then determined by detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of particularly useful chemiluminescent labeling compounds are luminol, isoluminol, theromatic acridinium ester, 5 imidazole, acridinium salt and oxalate ester.

Likewise, a bioluminescent compound may be used to label the antibody of the present invention. Bioluminescence is a type of chemiluminescence found in biological systems in which a catalytic protein increases the efficiency of the chemiluminescent reaction. 10 The presence of a bioluminescent protein is determined by detecting Important bioluminescent compounds the presence of luminescence. for purposes of labeling are luciferin, luciferase and aequorin.

An antibody molecule of the present invention may be adapted for utilization in a immunometric assay, also known as a 15 "two-site" or "sandwich" assay. In a typical immunometric assay, a quantity of unlabeled antibody (or fragment of antibody) is bound to a solid support or carrier and a quantity of detectably labeled soluble antibody is added to permit detection and/or quantitation of the ternary complex formed between solid-phase antibody, antigen, and labeled antibody.

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Typical, and preferred, immunometric assays include "forward" assays in which the antibody bound to the solid phase is first contacted with the sample being tested to extract the antigen form the sample by formation of a binary solid phase antibody-antigen 25 complex. After a suitable incubation period, the solid support or carrier is washed to remove the residue of the fluid sample, including unreacted antigen, if any, and then contacted with the solution containing an unknown quantity of labeled antibody (which functions as a "reporter molecule"). After a second incubation 30 period to permit the labeled antibody to complex with the antigen bound to the solid support or carrier through the unlabeled antibody, the solid support or carrier is washed a second time to remove the unreacted labeled antibody.

In another type of "sandwich" assay, which may also be 35 useful with the antigens of the present invention, the so-called "simultaneous" and "reverse" assays are used. A "simultaneous" and "reverse" assays are used. A simultaneous assay involves a single

incubation step as the antibody bound to the solid support or carrier and labeled antibody are both added to the sample being tested at the same time. After the incubation is completed, the solid support or carrier is washed to remove the residue of fluid sample and uncomplexed labeled antibody. The presence of labeled antibody associated with the solid support or carrier is then determined as it would be in a conventional "forward" sandwich assay.

In the "reverse" assay, stepwise addition first of a solution of labeled antibody to the fluid sample followed by the addition of unlabeled antibody bound to a solid support or carrier after a suitable incubation period is utilized. After a second incubation, the solid phase is washed in conventional fashion to free it of the residue of the sample being tested and the solution of unreacted labeled antibody. The determination of labeled antibody associated with a solid support or carrier is then determined as in the "simultaneous" and "forward" assays. See, e.g., for the abovementioned immunological techniques, Harlow, <a href="supra">supra</a>; Ausubel et al, <a href="supra">supra</a>; and Sambrook et al, <a href="supra">supra</a>. GPR polypeptides of the present invention can be made by chemical synthesis or by recombinant methods, wherein chemical synthesis is preferred.

Synthetic production of transmembrane proteins of the present invention

GPR polypeptides, variants and chemical derivatives thereof can be synthesized according to known method steps, including portions of known GPR transmembrane domains, consensus peptides thereof, conservative substitution derivative thereof or functional derivatives thereof.

Chemical polypeptide synthesis is a rapidly evolving area in the art, and methods of solid phase polypeptide synthesis are well-described in the following references, hereby entirely incorporated by reference: (Merrifield, B., J. Amer. Chem. Soc. 85:2149-2154 (1963); Merrifield, B., Science 232:341-347 (1986); Wade, J.D. et al., Biopolymers 25:S21-S37 (1986); Fields, G.B., Int. J. Polypeptide Prot. Res. 35:161 (1990); MilliGen Report Nos. 2 and 2a, Millipore Corporation, Bedford, MA, 1987) Ausubel et al, supra, and Sambrook et al. supra.

In general, as is known in the art, such methods involve blocking or protecting reactive functional groups, such as free amino, carboxyl and thio groups. After polypeptide bond formation, the protective groups are removed (or de-protected). Thus, the addition of each amino acid residue requires several reaction steps for protecting and deprotecting. Current methods utilize solid phase synthesis, wherein the C-terminal amino acid is covalently linked to an insoluble resin particle large enough to be separated from the fluid phase by filtration. Thus, reactants are removed by washing the resin particles with appropriate solvents using an automated programmed machine. The completed polypeptide chain is cleaved from the resin by a reaction which does not affect polypeptide bonds.

In the more classical method, known as the "tBoc method," the amino group of the amino acid being added to the resin-bound 15 C-terminal amino acid is blocked with tert-butylox/carbonyl chloride This protected amino acid is reacted with the bound amino acid in of the the condensing presence dicyclohexylcarbodiimide, allowing its carboxyl group to form a polypeptide bond the free amino group of the bound amino acid. amino-blocking group is then removed by acidification with trifluoroacetic acid (TFA); it subsequently decomposes into gaseous carbon dioxide and isobutylene. These steps are repeated cyclically for each additional amino acid residue. A more vigorous treatment with hydrogen fluoride (HF) or trifluoromethanesulfonyl derivatives 25 is common at the end of the synthesis to cleave the benzyl-derived side chain protecting groups and the polypeptide-resin bond.

More recently, the preferred "Fmoc" technique has been introduced as an alternative synthetic approach, offering milder reaction conditions, simpler activation procedures and compatibility 30 with continuous flow techniques. This method was used, e.g., to prepare the peptide sequences disclosed in the present application. Here, the  $\alpha$ -amino group is protected by the base labile 9-fluorenylmethoxycarbonyl (Fmoc) group. The benzyl side chain protecting groups are replaced by the more acid labile t-butyl derivatives. Repetitive acid treatments are replaced by deprotection with mild base solutions, e.g., 20% piperidine in dimethylformamide (DMF), and the final HF cleavage treatment is eliminated. A TFA

solution is used instead to cleave side chain protecting groups and the polypeptide resin linkage simultaneously.

At least three different polypeptide-resin linkage agents can be used: substituted benzyl alcohol derivatives that can be cleaved with 95% TFA to produce a polypeptide acid, methanolic ammonia to produce a polypeptide amide, or 1% TFA to produce a protected polypeptide which can then be used in fragment condensation procedures, as described by Atherton, E. et al., J. Chem. Soc. Perkin Trans. 1:538-546 (1981) and Sheppard, R.C. et al., Int. J. 10 Polypeptide Prot. Res. 20:451-454 (1982). Furthermore, highly reactive Fmoc amino acids are available as pentafluorophenyl esters or dihydro-oxobenzotriazine esters derivatives, saving the step of activation used in the tBoc method.

Sequences available to use as a basis for polypeptide 15 synthesis can be based on published sequences of G-protein coupled receptors, ligands and/or effectors, wherein the transmembrane or functional domains correspond to sections of hydrophobic or other amino acids of 5 to 100 amino acids, such as 5-10, 10-15, 15-25, 20-25, 23-27, 25-30, 28-35, 20-40, 10-40, 20-30, 30-40, 40-50, 10-80, 20 20-60 or 25-40 amino acids in length. Recombinant production of GPR polypeptides can be accomplished according to known method steps. Standard reference works setting forth the general principles of recombinant DNA technology include Watson, J.D. et al., Molecular Biology of the Gene, Volumes I and II, The Benjamin/Cummings 25 Publishing Company, Inc., publisher, Menlo Park, CA (1987); Darnell, J.E. et al., Molecular Cell Biology, Scientific American Books, Inc., publisher, New York, NY (1986); Lewin, B.M., Genes III, John Wiley & Sons, publishers, New York, NY (1989); Old, R.W., et al., Principles of Gene Manipulation: An Introduction to Genetic 30 Engineering, 2d edition, University of California Press, publisher, Berkeley, CA (1981); Ausubel et al, eds., Current Protocols in Molecular Biology, Wiley Interscience, publisher, New York, NY (1987, 1992); and Sambrook et al., Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory, publisher, Cold 35 Spring Harbor, NY (1989), the entire contents of which references are herein incorporated by reference.

A nucleic acid sequence encoding a GPR polypeptide of the present invention may be recombined with vector DNA in accordance techniques, including conventional with staggered-ended termini for ligation, restriction enzyme digestion 5 to provide appropriate termini, filling in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and ligation with appropriate ligases. Techniques for such manipulations are disclosed, e.g., by Ausubel et al, supra, and are well known in the art.

A nucleic acid molecule, such as DNA, is said to be 10 "capable of expressing" a polypeptide if it contains nucleotide sequences which contain transcriptional and translational regulatory information and such sequences are "operably linked" to nucleotide sequences which encode the polypeptide. An operable linkage is a 15 linkage in which the regulatory DNA sequences and the DNA sequence sought to be expressed are connected in such a way as to permit gene expression as GPR polypeptides in recoverable amounts. The precise nature of the regulatory regions needed for gene expression may vary from organism to organism, as is well known in the analogous art. 20 See, e.q., Sambrook, supra and Ausubel supra.

present invention accordingly encompasses expression of a GPR polypeptide, in either prokaryotic or eukaryotic cells, although eukaryotic expression is preferred.

Preferred hosts are bacterial or eukaryotic hosts including 25 bacteria, yeast, insects, fungi, bird and mammalian cells either in vivo, or in situ, or host cells of mammalian, insect, bird or yeast It is preferred that the mammalian cell or tissue is of human, primate, hamster, rabbit, rodent, cow, pig, sheep, horse, goat, dog or cat origin, but any other mammalian cell may be used.

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Further, by use of, for example, the yeast ubiquitin hydrolase system, in vivo synthesis of ubiquitin-transmembrane polypeptide fusion proteins may be accomplished. The fusion proteins so produced may be processed in vivo or purified and processed in vitro, allowing synthesis of a GPR polypeptide of the present 35 invention with a specified amino terminus sequence. Moreover, problems associated with retention of initiation codon-derived methionine residues in direct yeast (or bacterial) expression may be

avoided. Sabin et al., *Bio/Technol*. 7(7): 705-709 (1989); Miller et al., *Bio/Technol*. 7(7): 698-704 (1989).

Any of a series of yeast gene expression systems incorporating promoter and termination elements from the actively sexpressed genes coding for glycolytic enzymes produced in large quantities when yeast are grown in mediums rich in glucose can be utilized to obtain GPR polypeptides of the present invention. Known glycolytic genes can also provide very efficient transcriptional control signals. For example, the promoter and terminator signals of the phosphoglycerate kinase gene can be utilized.

Production of GPR polypeptides or functional derivatives thereof in insects can be achieved, for example, by infecting the insect host with a baculovirus engineered to express transmembrane polypeptide by methods known to those of skill. See Ausubel et al, eds. Current Protocols in Molecular Biology, Wiley Interscience, §§16.8-16.11 (1987, 1992).

In a preferred embodiment, the introduced nucleotide sequence will be incorporated into a plasmid or viral vector capable of autonomous replication in the recipient host. Any of a wide variety of vectors may be employed for this purpose. See, e.g., Ausubel et al, <a href="mailto:supra">supra</a>, <a href="mailto:supra">s</a>, <a href=

Preferred prokaryotic vectors known in the art include

30 plasmids such as those capable of replication in <u>E. coli</u> (such as, for example, pBR322, ColE1, pSC101, pACYC 184, \piVX). Such plasmids are, for example, disclosed by Maniatis, T., et al. (Molecular Cloning, A Laboratory Manual, Second Edition, Cold Spring Harbor Press, Cold Spring Harbor, NY (1989); Ausubel et al, eds., Current

35 Protocols in Molecular Biology, Wiley Interscience, New York, NY (1987, 1992)). <u>Bacillus</u> plasmids include pC194, pC221, pT127, etc. Such plasmids are disclosed by Gryczan, T. (In: The Molecular

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Biology of the Bacilli, Academic Press, NY (1982), pp. 307-329).
Suitable Streptomyces plasmids include pIJ101 (Kendall, K.J., et al.,
J. Bacteriol. 169:4177-4183 (1987)), and streptomyces bacteriophages
such as φC31 (Chater, K.F., et al., In: Sixth International
Symposium on Actinomycetales Biology, Akademiai Kaido, Budapest,
Hungary (1986), pp. 45-54). Pseudomonas plasmids are reviewed by
John, J.F., et al. (Rev. Infect. Dis. 8:693-704 (1986)), and Izaki,
K. (Jpn. J. Bacteriol. 33:729-742 (1978); and Ausubel et al, supra).

The expressed protein may be isolated and purified in 10 accordance with conventional conditions, such as extraction, precipitation, chromatography, affinity chromatography, electrophoresis, or the like. For example, the cells may be collected by centrifugation, or with suitable buffers, lysed, and the protein isolated by column chromatography, for example, 15 DEAE-cellulose, phosphocellulose, polyribocytidylic acid-agarose. hydroxyapatite or by electrophoresis or immunoprecipitation. Alternatively, the transmembrane polypeptide or functional derivative thereof may be isolated by the use of anti-transmemorane polypeptide antibodies. Such antibodies may be obtained by well-known methods, 20 some of which are mentioned below. These antibodies may be immobilized on cellulose, agarose, hollow fibers, or cellulose filters by covalent chemical derivatives by methods well known to those skilled in the art.

As discussed herein, GPR polypeptides of the present invention may be further modified for purposes of drug design, such as for example to reduce immunogenicity, to prevent solubility and/or enhance delivery, or to prevent clearance or degradation.

Appropriate modification of the primary amino acid sequence of GPR polypeptides of the present invention, obtained by mutagenesis or utilizing fragments of other related forms of G-protein transmembrane proteins, as described herein, will allow the creation of molecules which bind G-protein coupled receptors with higher affinity than that exhibited by naturally occurring transmembrane domains. Small polypeptides that are provided according to the present invention which polypeptides maintain G-protein coupled receptor binding inhibition activity, are expected to have two

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advantages over larger polypeptides. These advantages include (1) greater stability and diffusibility, and (2) less immunogenicity.

Since polypeptides according to the present invention are generally small (10-40, 20-30, 15-25, 30-45 amino acids), cell or 5 tissue sources of G-protein coupled receptors are not required to . practice the present invention, since known polypeptide syntheses steps can be used without undue experimentation to provide GPR polypeptides or sequences substantially corresponding thereto.

## Pharmaceutical Preparations

Preparations of GPR polypeptides for administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions, which may contain auxiliary agents or excipients which are known in the art. Pharmaceutical compositions such as tablets and capsules can also be prepared according to 15 routine methods.

By the term "protection" from infection or disease as used herein is intended "prevention," "suppression" or "treatment." "Prevention" involves administration of a GPR polypeptide. polypeptide derivative, or anti-idiotypic antibody prior to the 20 <u>induction</u> of the disease.

"Suppression" involves administration of the composition prior to the clinical appearance of the disease.

"Treatment" involves administration of the protective composition after the appearance of the disease. 25 understood that in human and veterinary medicine, it is not always possible to distinguish between "preventing" and "suppressing" since the ultimate inductive event or events may be unknown, latent, or the patient is not ascertained until well after the occurrence of the Therefore, it is common to use the term event or events. "prophylaxis" as distinct from "treatment" to encompass both . "preventing" and "suppressing" as defined herein. The term "protection," as used herein, is meant to include "prophylaxis."

At least one GPR polypeptide, antibody or anti-idiotypic antibody of the present invention may be administered by any means 35 that achieve their intended purpose, for example, to treat GPR related pathologies, such as psychotic disorders, schizophrenia, by inhibition of binding of Dopamine D, receptors

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using a GPR polypeptide corresponding to a fragment or consensus portion of a dopamine  $D_2$  transmembrane domain; in the form of a pharmaceutical composition.

For example, administration of such a composition may be by various parenteral routes such as subcutaneous, intravenous, intradermal, intramuscular, intraperitoneal, intranasal, transdermal, or buccal routes. Alternatively, or concurrently, administration may be by the oral route. Parenteral administration can be by bolus injection or by gradual perfusion over time.

A preferred mode of using a GPR pharmaceutical composition of the present invention is by intravenous or parenteral application.

A typical regimen for preventing, suppressing, or treating G-protein coupled receptor pathologies, such as dopamine receptor related schizophrenia, comprises administration of an effective amount of a GPR polypeptide, consensus sequence, or chemical derivative thereof, administered over a period of one or several days, up to and including between one week and about 24 months.

It is understood that the dosage of a GPR polypeptide of the present invention administered in vivo or in vitro will be dependent upon the age, sex, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired. The ranges of effective doses provided below are not intended to limit the inventors and represent preferred dose ranges. However, the most preferred dosage will be tailored to the individual subject, as is understood and determinable by one of skill in the art, without undue experimentation.

The total dose required for each treatment may be administered by multiple doses or in a single dose. a GPR polypeptide or functional a chemical derivative thereof may be administered alone or in conjunction with other therapeutics directed to GPR related pathologies, such as a the dopamine receptor related pathology as a non limiting example, or directed to other symptoms of the disease.

Effective amounts of the a GPR polypeptide or composition, which may also include a functional derivative thereof, or a GPR anti-idiotypic antibody, are from about 0.01  $\mu g$  to about 100 mg/kg body weight, and preferably from about 10  $\mu g$  to about 50 mg/kg body

weight, such 0.05, 0.07, 0.09, 0.1, 0.5, 0.7, 0.9, 1, 2, 5, 10, 20, 25, 30, 40, 45, or 50 mg/kg.

Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions, which may contain auxiliary agents or excipients which are known in the art. Pharmaceutical compositions such as tablets and capsules can also be prepared according to routine methods.

Pharmaceutical compositions comprising at least one GPR polypeptide of the present invention may

include all compositions wherein the GPR polypeptide is contained in an amount effective to achieve its intended purpose. In addition to the GPR polypeptide, a pharmaceutical composition may contain suitable pharmaceutically acceptable carriers, such as comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically.

Pharmaceutical compositions include suitable solutions for administration intravenously, subcutaneously, dermally, orally, mucosally, rectally or may by injection or orally, and contain from about 0.01 to 99 percent, preferably from about 20 to 75 percent of active component (i.e. the antibody) together with the excipient. Pharmaceutical compositions for oral administration include tablets and capsules. Compositions which can be administered rectally include suppositories.

## Example 1: Synthesis of a G-Protein Transmembrane Polypeptide and 25 Consensus Polypeptide

The polypeptides in Figs. 1-5 were synthesized using the following procedure and include the following characteristics.

Peptide I (SEQ ID NO:1), as shown in Fig. 1, was used as a control for hydrophobic interaction alone as the mechanism of binding and was run in parallel with the test polypeptides described below. Polypeptide II (SEQ ID NO:2), as shown in Fig. 2, represents a membrane-spanning fragment of transmembrane segment III in the dopamine  $D_2$  receptor. This particular fragment was chosen since it has been implicated in the  $\beta$ -adrenergic receptor as having many residues which are involved in ligand binding interaction.

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Polypeptide III (SEQ ID NO:3), as shown in Fig. 3, represents the consensus polypeptide which was developed as a model for the dopamine  $D_2$  system and polypeptide IV (SEQ ID NO:4), as shown in Fig. 4, is a control for length dependence to show how critical the polypeptide length is in binding studies. Polypeptide V (SEQ ID NO:5), as shown in Fig. 5, is a consensus sequence of transmembrane domains of dopamine receptors  $D_1$  and  $D_2$ .

The above polypeptides I-V (SEQ ID NOS:1-5), as shown in Figs. 1-5, respectively, were synthesized using solid phase synthesis 10 on a Milligen 9600 polypeptide synthesizer using Fmoc amino acids (provided by Milligen/Biosearch) and PALpolystyrene (Milligen/Biosearch). Coupling times were 1 hour and the polypeptides were cleaved bу trifluoroacetic acid/phenol/H2O/thioanisole/ethanedithiol (82.5:5:5:5:2.5) at room 15 temperature for 2 hours. The filtrate was collected and washed with 2 mL of trifluoroacetic acid (TFA) and 1 mL of dichloromethane (DCM). The filtrate was reduced in vacuo to 2 ml in volume and the resulting polypeptide was precipitated out by the addition of water. polypeptides were then dissolved in 1,1,1,3,3,3-hexafluoro-2-propanol 20 [(HFIP) lyophilized; and stored at Eastman]; purification. Polypeptides I-V (SEQ ID NOS:1-5), were purified using reverse-phase HPLC using a preparative Vydac C4 column (Vydac) at 60°C at a flow rate of 6.0 mL/min with a linear gradient of 0-100% B in a 60 min period at a UV detection wavelength of 275 nm.

Due to the highly hydrophobic nature of these polypeptides, methanol was used with 0.1% (W/V) TFA and 0.5% (W/V) HFIP as solvent A and 2-propanol with 0.1% TFA as solvent B, in order to purify these polypeptides. Further purification was performed with an analytical C4 column (Vydac) with an isocratic gradient of 40% B at a flow rate of 1 ml/min. Identity of the polypeptides was confirmed by Fast-atom bombardment mass spectrometry and electrospray mass spectrometry and amino acid analysis. Stock solutions of polypeptides were made in HFIP and stored at -20°- 80°C.

Circular Dichroism (CD). Spectra were recorded on an Aviv model 60 DS circular dichroism spectrophotometer at room temperature with a 1 cm by 1 mm cell. The amplitude of the CD signal was calibrated using 1 0.1% (w/v) solution of d (+)-camphorsulfonic acid

(Aldrich) and the wavelength of the CD signal was set using standard absorbance peaks of benzene vapor. Polypeptide concentrations were determined in a Cary 210 UV spectrophotomer with the absorbance measured at 280 nm. Helical content was estimated using CD signal intensity according to the method of Chen. et al <u>Biochem</u>. 13:3350-3359 (1974). This calculation compares the experimental ellipticity at 222 nm ([0]222) ([0]) to a theoretical [0]222. The theoretical [0]222 is empirically adjusted to account for differences in polypeptide length and is based on experimental CD data from a series of proteins with known crystal structures. Since both the curve shape and magnitude are important in analysis of a CD spectrum for secondary structure contributions, we also considered qualitatively the contributions to the spectral shapes from different secondary structures using reference curves for poly (L-lysine).

Fig. 6 shows a CD spectrum of the consensus polypeptide III (SEQ ID NO:3) demonstrating that the polypeptide III is only partially helical in a solvent system in which most membrane polypeptides are strongly helical.

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Preparation of Small Unilamellar Vesicles. Polypeptides

were incorporated into DMPC vesicles at lipid:peptide ratio of 147:1
in the following manner: polypeptide in HFIP was mixed with
dimyrystyroyl- phosphatidylcholine (synthetic) (DMPC) in dry
chloroform and dried to a film with a stream of dry nitrogen at 0°C.
This residue was then dried further overnight under a vacuum (1 x 10²
torr). The residue was then hydrated in 100 mM NaCl and sonicated
for a 30-min period under nitrogen at 0°C. The suspension was
sedimented for a 30-min at 100,000 g (4°C) to remove any residual
titanium particles and large unilamellar vesicles. The supernatant
was removed and sedimented once more at 159,000 g for a 45 min period
at 4°C. The supernatant in the lower portion was used immediately.
This basic procedure has been shown to reliably produce small
unilamellar vesicles.

Radioligand Binding Assays. A 0.50 mL volume of 1.00 nM [3H]-spiperone (New England specific activity 21.4 Ci/mmol) was added to assay tubes which contained 0.5 mL lipid/peptide supernatant, 0.5 mL Tris buffer pH 7.4 and 0.5 mL of cold drug for a final volume of 2.0 mL. Nonspecific binding was defined in the presence of 1 uM of

(+) butaclamol or 1 uM spiperone. Appropriate controls for lipid vesicles containing no polypeptide were also run. Assay tubes were prepared in triplicate and the mixture was incubated for 1 h at 25°C. Incubation was terminated by filtration through filters presoaked in 5 0.1% polyethyleneimine (w/v, Sigma) for at least 1 h prior to use.

Filters were then washed with 6.0 mL of cold 50 mM Tris-HCl buffer, pH 7.40. For detection of radioactivity, filters were placed in 2.0 mL of scintillation fluid (Scintiverse) and incubated for 24 h. The activity of the tritium was determined in a Beckman LS 7500 liquid scintillation counter. Specific binding of [3H]-spiperone was defined as the difference in binding in the presence and absence of unlabeled (+) butaclamol.

Fig. 7 shows results of radioligand binding assays comparing polypeptide I (SEQ ID NO:1) as a control unit polypeptide III (SEQ ID NO:3) according to the present invention. Polypeptide III (SEQ ID NO:3) is shown to unexpectedly provide receptor-like functional binding, as demonstrated by binding to the neuroleptic agent, spiperone, into a stereoselective, concentration-dependent manner.

It has also been demonstrated that as little as 0.1% of a GPR polypeptide according to the present invention is able to form a receptor-like functional binding site. Thus, a GPR polypeptide of the present invention is unexpectedly shown to act both as GPR ligands and GPR binding sites.

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All references cited herein, including journal articles or abstracts, published or corresponding U.S. or foreign patent applications, issued U.S. or foreign patents, or any other references, are entirely incorporated by reference herein, including all data, tables, figures, and text presented in the cited references. Additionally, the contents of the references cited within the references cited herein are also entirely incorporated by reference.

Reference to known method steps, conventional methods steps, known methods or conventional methods is not in any way an admission that any aspect, description or embodiment of the present invention is disclosed, taught or suggested in the relevant art.

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The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying knowledge within the skill of the art (including the contents of the references cited herein), readily modify and/or adapt for various applications such specific embodiments, without undue experimentation, without departing from the generic concept of the present invention. Therefore, such adaptations and modifications are intended to be comprehended within the meaning and range of equivalents of the disclosed embodiments, based on the teaching and guidance presented herein. It is to be understood that the phraseology or terminology herein is for the purpose of description and not of limitation, such that the terminology or phraseology of the present specification is to be interpreted by the skilled artisan in light of the teachings and guidance presented herein.

PCT/US93/08528

- 55 -

## SEQUENCE LISTING

```
(1) GENERAL INFORMATION:
          (i) APPLICANT: Murphy, Randall B.
                          Schuster, David I.
         (ii) TITLE OF INVENTION: POLYPEPTIDES OF G-COUPLED RECEPTOR PROTEINS, AND
 5
    COMPOSITIONS AND METHODS THEREOF
        (iii) NUMBER OF SEQUENCES: 95
         (iv) CORRESPONDENCE ADDRESS:
               (A) ADDRESSEE: BROWDY AND NEIMARK(B) STREET: 419 Seventh Street, N.W.
10
               (C) CITY: Washington
               (D) STATE: D.C.
               (E) COUNTRY: USA
(F) ZIP: 20004
15
          (v) COMPUTER READABLE FORM:
                (A) MEDIUM TYPE: Floppy disk
               (B) COMPUTER: IBM PC compatible (C) OPERATING SYSTEM: PC-DOS/MS-DOS
               (D) SOFTWARE: PatentIn Release #1.0, Version #1.25
         (vi) CURRENT APPLICATION DATA:
20
                (A) APPLICATION NUMBER: US 07/943,236
               (B) FILING DATE: 10-SEP-1992
                (C) CLASSIFICATION:
       (viii) ATTORNEY/AGENT INFORMATION:
25
                (A) NAME: Townsend, Kevin G.
                (B) REGISTRATION NUMBER: 34,033
                (C) REFERENCE/DOCKET NUMBER: MURPHY=2
         (ix) TELECOMMUNICATION INFORMATION:
                (A) TELEPHONE: 202-628-5197
30
                (B) TELEFAX: 202-737-3528
                (C) TELEX: 248633
     (2) INFORMATION FOR SEQ ID NO:1:
          (i) SEQUENCE CHARACTERISTICS:
                (A) LENGTH: 24 amino acids
                (B) TYPE: amino acid
35
                (C) STRANDEDNESS: single
                (D) TOPOLOGY: linear
         (ii) MOLECULE TYPE: peptide
         (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:
          Leu Ser Leu Leu Ser Leu Leu Ser Leu Leu Ser Leu Leu Ser
40
          1
                           5
          Leu Leu Ser Leu Tyr Tyr Tyr
                       20
     (2) INFORMATION FOR SEQ ID NO:2:
45
           (i) SEQUENCE CHARACTERISTICS:
                (A) LENGTH: 27 amino acids
                (B) TYPE: amino acid
                (C) STRANDEDNESS: single
                (D) TOPOLOGY: linear
50
          (ii) MOLECULE TYPE: peptide
          (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:
          Asp Asp Ile Phe Val Thr Leu Asp Val Leu Phe Ser Thr Ala Ser Ile
          Leu Asn Leu Ser Ala Ile Ser Leu Lys Lys
55
                       20
```

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5	(2)	INFOR (i)	SEQU (A) (B) (C) (D)	ENCE LEN TYP: STR. TOP	CHA GTH: E: a ANDE OLOG	RACT 26 mino DNES Y: 1	ERIS amin aci S: s inea	TICS o ac d ingl r	ids								
10		(xi) Asp 1	SEQU Tyr	ENCE Ala	Ile	CRIP Phe 5	TION Val	: SE Leu	Q ID Tyr	NO: Ala	3: Ser 10	Ala	Trp	Leu	Ser	Phe 15	Asn
		Cys	Pro		Ile 20	Val	Thr	Leu	naA	11e 25	Lys						
15	(2)		SEQU (A) (B) (C) (D)	ENCE LEN TYP STR TOP	CHA GTH: E: a ANDE OLOG	RACT 16 mino DNES Y: 1	ERIS amin aci S: s inea	TICS o ac d ingl r	ids								
20		(xi)	SEQU Ala	ENCE	DES	CRIF	TION	: SE	Q ID Ile	NO: Val	4: Ser 10	Phe	Tyr	Val	Phe	Ile 15	Asp
25	(2)	(i)	SEQU (A) (B) (C)	ENCE LEN TYP STR TOP	CHA GTH: E: a LANDE POLOG	RACT 27 umino EDNES Y: ]	TERIS  amin  aci  SS: s  inea	TICS o ac d ingl	ids								
30		(xi) Asp 1	SEQU Cys	Asp ENCE	DES Val	CRII Phe 5	PTION Val	I: SE Phe	Q II Val	OM ( Asp	:5: Ile 10	Met	Leu	Cys	Thr	Ala 15	Ser
		Ile	Phe	Asn	Leu 20	Cys	Ala	Ile	Ser	<b>V</b> al 25	Gly	Lys					
35	(2)		SEQU (A) (B)	JENCE LEN TYI	CHA IGTH: PE: 8	ARAC : 31	reris 7 ami 5 aci	ino a	cida	5							
40		(ii)		TOE	OLO	3Y: :	SS: s linea pepti	ar	Le								
		(xi) Ser 1	SEQ( Leu	JE <b>N</b> CE Val	DES Leu	SCRII Leu 5	PTION Leu	N: SI Phe	EQ II Ala	NO Asp	:6: Phe 10	Ser	Ser	Met	Leu	Gly 15	Cys
45		Met	Ala	Val	Leu 20	Ile	Gly	Phe	Trp	Arg 25	Leu	Lys	Leu	Leu	Arg 30	Asn	His
		Val	Thr	Lys 35	Val	Ile	Ala	Cys	Phe 40	Сув	Ala	Thr	Ser	Phe 45	Cys	Lys	qaA
50		Phe	Pro 50	Ser	Thr	Ile	Leu	Thr 55	Leu	Thr	Asn	Thr	Ala 60	Val	Asn	Gly	Gly
		Phe	Pro	Cys	Tyr	Leu	Tyr	Ala	Ile	Val	Ile	Thr 75	Tyr	Gly	Ser	Phe	Ala 80

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		Cys	Trp	Leu	Trp	Thr 85	Leu	Ile	Cys	Leu	Ala 90	Ile	Ser	Ile	Tyr	Met 95	Leu
		Ile	Val	Lys	Arg 100	Glu	Pro	Glu	Pro	Glu 105	Leu	Phe	Glu	Lys	Tyr 110	Tyr	Tyr
5		Leu	Leu	Cys 115	Trp	Gly	Leu	Pro	Leu 120	Ile	Ser	Thr	Ile	Gly 125	Leu	Lys	Asn
		Thr	Val 130	Gln	Phe	Val	Gly	Asn 135	Trp	Cys	Trp	Ile	Gly 140	Val	Ser	Phe	Thr
LO		Gly 1 <b>4</b> 5	Tyr	Arg	Phe	Gly	Leu 150	Phe	Tyr	Pro	Phe	Leu 155	Phe	Ile	Trp	Ala	Ile 160
		Ser	Ala	Val	Leu	Val 165	Gly	Leu	Thr	Ser	Arg 170	Tyr	Thr	Tyr	Trp	Ile 175	His
		Asn	Gly	Val	Ser 180	Asp	Asn	Lys	Glu	Lys 185	His	Leu	Thr	Tyr	Gln 190	Phe	Lys
L5		Leu	Ile	Asn 195	Tyr	Ile	Ile	Val	Phe 200	Leu	Val	Cys	Trp	Val 205	Phe	Ala	Val
		Val	Asn 210	Arg	Ile	Val	naA	Gly 215	Leu	Asn	Trp	Pro	Pro 220	Ala	Leu	Asn	Ile
20		Leu 225	His	Thr	Tyr	Leu	Ser 230	Val	Ser	His	Gly	Phe 235	Trp	Ala	Ser	Val	Thr 240
		Phe	Ile	Tyr	Asn	Asn 2 <b>4</b> 5	Pro	Leu	Met	Trp	Arg 250	Tyr	Phe	Gly	Ala	Lys 255	Ile
		Leu	Thr	Val	Phe 260	Thr	Phe	Phe	Gly	Tyr 265	Phe	Thr	Asp	Val	Gln 270	Lys	Lys
25		Leu	Glu	Lys 275	Asn	Leu	Ser	Pro	<b>Tyr</b> 280	Ser	Ser	Ser	Arg	Gly 285	Thr	Ser	Gly
		Lys	Thr 290	Met	Leu	Gly	His	Pro 295	Thr	Gly	Asp	Asp	Val 300	Gln	Сув	Ser	Ser
30		Asp 305	Leu	Gln	Cys	Ser	Leu 310	Glu	Arg	His	Pro	Asn 315	Met	Val			
35	(2)		SEQU (A) (B) (C) (D)	JENCI LEI TYI STI	CHI NGTH: PE: 8 RANDI POLO	ARAC : 349 amin SDNE SY:	FERIS  ami  aci  SS: s  linea	STICS ino a id sing: ar	acid	s							
		(ii) (xi)	SEQ	JENCI	E DES	CRI	PTIO	N: SI									
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		Asn	Val	Leu	Val 20	Cys	Trp	Ala	Val	Trp 25	Leu	Asn	Ser	Asn	Leu 30	Asn	Val
		Thr	Asn	Tyr 35	Phe	Val	Val	Ser	Leu 40	Ala	Ala	Ala	Asp	Ile 45	Ala	Val	Gly
45		Val	·Ile 50	Ala	Ile	Pro	Phe	Ala 55	Ile	Thr	Ile	Ser	Thr 60	Gly	Phe	Сув	Ala
		Ala	Cys	His	Asn	Cys	Leu	Phe	Phe	Ala	Cys	Phe	Val	Leu	Val	Leu	Thr

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		65					70					75					80
		Gln	Ser	Ser	Ile	Phe 85	Ser	Leu	Leu	Ala	Ile 90	Ala	Ile	Asp	Arg	Tyr 95	Ile
5		Ala	Ile	Arg	Ile 100	Pro	Leu	Arg	Tyr	Asn 105	Gly	Leu	Val	Thr	Gly 110	Thr	Arg
		Ala	Lys	Gly 115	Ile	Ile	Ala	Val	Cys 120	Trp	Val	Leu	Ser	Phe 125	Ala	Ile	Gly
			130	Pro				135					140				
LO		145		Tyr			150					155					160
				Val		165					170					1/5	
15				Leu	180					185					190		
				Arg 195					200					205			
			210	Arg				215					220				
20		225		Val			230					235					240
				Phe		245					250					255	
25				Tyr	260					265					270		
				Tyr 275					280					285			
			290					295					300				
30		305		Ser			310					315					320
		Ile	Ser	Leu	Arg	Leu 325		Gly	His	Pro	330	Gly	Val	Trp	Ala	. Asn 335	Gly
35		Ser	Ala	Pro	340		Glu	Arg	Arg	345		Gly	Тут	Thr			
40	(2)	INFO	SE( ( <i>I</i> (E	TION QUENCAL A) LE B) TY C) ST C) TO	E CH INGTH IPE: IRANI	IARAC I: 31 amir EDNE	TERI 4 am 10 ac SSS:	STIC nino cid sing	CS: acid	ls							
		(xi)	MOI	LECUI	E TY	PE:	pept PTIC	ide ON: 9	SEO I	D NO	D:8:						
45		Ala 1	ту:	r Ile	e Gly	7 <b>Il</b> e 5	e Glu	ı Val	l Lei	ı Ile	e Ala 10					15	
		Trp	Le	u Val	1 11e 20	Tr	Ala	a Vai	l Lys	s Val 25	l Ası	n Glr	n Ala	a Lei	1 Arg	j Asp	Ala

		Thr	Phe	Сув 35	Phe	Ile	Val	Ser	Ile 40	Ala	Val	Ala	Asp	Val 45	Ala	Val	Gly
		Ala	Leu 50	Val	Ile	Pro	Leu	Ala 55	Ile	Leu	Ile	Asn	Ile 60	Gly	Pro	Arg	Thr
5		Tyr 65	Phe	His	Thr	аұЭ	Leu 70	Met	Val	Ala	Cys	Pro 75	Val	Leu	Ile	Leu	Thr 80
		Gln	Ser	Ser	Ile	Ile 85	Ala	Leu	Leu	Ala	Ile 90	Ala	Val	Asp	Arg	Tyr 95	Leu
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		Ala	Ala	<b>Val</b> 115	Ala	Ile	Ala	Gly	Cys 120	Trp	Ile	Leu	Ser	Phe 125	Val	Val	Gly
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		Glu	Lys	Val	Ile	Ser 165	Met	Glu	Tyr	Met	<b>Val</b> 170	Tyr	Phe	Asn	Phe	Phe 175	Val
20		Trp	Val	Leu	Pro 180	Pro	Leu	Leu	Leu	Met 185	Val	Leu	Ile	Tyr	Leu 190	Glu	Val
		Phe	Tyr	Leu 195	Ile	Arg	Arg	Gln	Leu 200	Gly	Lys	Lys	Val	Ser 205	Ala	Ser	Ser
		Gly	Asp 210	Pro	Gln	Lys	Tyr	Tyr 215	Gly	Lys	Glu	Leu	Lys 220	Ile	Ala	Lys	Ser
25		Leu 225	Ala	Leu	Ile	Leu	Phe 230	Leu	Phe	Ala	Leu	Ser 235	Trp	Leu	Pro	Leu	His 240
		Ile	Ile	naA	Сув	11e 245	Thr	Leu	Phe	Суѕ	Pro 250	Ser	Cys	Arg	Lys	Pro 255	Ser
30		Ile	Leu	Met	<b>Tyr</b> 260	Ile	Ala	Ile	Phe	Leu 265	Thr	His	Gly	Asn	Ser 270	Ala	Met
		Pro	Ile	Val 275	Tyr	Ala	Phe	Arg	Ile 280	Gln	Lys	Phe	Arg	Val 285	Thr	Phe	Leu
		Lys	Ile 290	Trp	Asn	qaA	His	Phe 295	Arg	Сув	Gln	Pro	Thr 300	Pro	Pro	Val	Дар
35		Glu 305		Pro	Pro		Glu 310		Pro	His	Asp						
<b>4</b> 0	(2)	INFO (i)	SEQ (A (B (C	ION : UENC: ) LE ) TY: ) ST: ) TO	e ch ngth pe: rand	ARAC : 34 amin EDNE	TERI 2 am o ac SS:	STIC ino id sing	acid	s							
			MOL	ECUL	E TY	PE:	pept	ide	EO I	D NO	:9:						
45		Val	Ala	Phe	Ile	Gly 5	Ile	Thr	Thr	Gly	Leu 10	Leu	Ser	Ile	Ala	Thr 15	Val
		Thr	Gly	Asn	Leu	Leu	Val	Leu	Ile	Ser	Phe	Lys	Val	Asn	Thr	Glu	Leu

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					20					25					30		
		Lys	Thr	Val 35	Asn	Asn	Tyr	Phe	Leu 40	Leu	Ser	Ile	Ala	Cys 45	Ala	Asp	Leu
5		Ile	Ile 50	Gly	Thr	Phe	Ser	<b>M</b> et 55	Leu	Tyr	Leu	Leu	<b>Met</b> 60	His	Trp	Ala	Leu
		Gly 65	Thr	Leu	Ala	Cys	Asp 70	Leu	Trp	Leu	Ala	Leu 75	qaA	Tyr	Val	Ala	Ser 80
		Asn	Ala	Ser	Val	Leu 85	Asn	Leu	Leu	Leu	Ile 90	Ser	Phe	qaA	Arg	Tyr 95	Phe
10		Ser	Val	Thr	Arg 100	Pro	Leu	Ser	Tyr	Arg 105	Ala	Lys	Arg	Thr	Pro 110	Arg	Arg
		Ala	Ala	Ile 115	Met	Ile	Gly	Ile	Ala 120	Trp	Leu	Val	Ser	Phe 125	Val	Leu	Trp
15		Ala	Pro 130	Ala	Ile	Leu	Phe	Trp 135	Gln	Tyr	Leu	Val	Gly 140	Glu	Arg	Thr	Met
		Leu 145	Ala	Gly	Gln	Сув	Tyr 150	Ile	Gln	Phe	Leu	Ser 155	Gln	Pro	Ile	Ile	Thr 160
		Phe	Gly	Thr	Ala	Met 165	Ala	Ala	Phe	Tyr	<b>M</b> et 170	Pro	Val	Thr	Vai	Met 175	Thr
20		Leu	Tyr	Trp	Arg 180	Ile	Tyr	Arg	Phe	Thr 185	Glu	Asn	Arg	Ala	Arg 190	Glu	Leu
		Gln	Gly	Ser 195	Glu	Thr	Pro	Gly	Lys 200	Gly	Gly	Gly	Ser	Ser 205	Ser	Ser	Ser
25		Glu	Arg 210	Ser	Gln	Pro	Gly	Ala 215	Glu	Gly	Ser	Pro	Glu 220	Thr	Pro	Lys	Gly
		Gln 225	Lys	Pro	Arg	Gly	Lys 230	Glu	Leu	Ala	Lys	Arg 235	Lys	Thr	Phe	Ser	Leu 240
		Val	Lys	Glu	Lys	Lys 245	Ala	Ala	Arg	Thr	Leu 250	Ser	Ala	Ile	Leu	Leu 255	Ala
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		Phe	Cys	Lys 275		Суз	Val		Glu 280		Leu	Trp	Glu	Leu 285		Tyr	Trp
35		Leu	Ile 290	_	Tyr	Val	Asn	Ser 295		Ile	Asn	Pro	Trp 300		Ala	Leu	Cys
		Asn 305		Ala	Phe	Arg	Asp 310		Phe	Arg	Leu	Leu 315	Leu	Leu	Сув	Trp	Asp 320
		Lys	Arg	Arg	Trp	Arg 325		Ile	Pro	Lys	330		Gly	Ser	Val	His 335	Arg
40		Thr	Pro	Ser	Arg 340		Сув	;									
<b>4</b> 5	(2)	INFC (i)	SEÇ (A	UENC LE LE	E CH NGTH PE:	ARAC U: 31 amin	TERI 7 au 10 ac	O:10 STIC nino cid sing	S: acid	ls							

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	(ii)		TOI ECULI													
5	(xi) Val 1		JENCI Phe								Leu	Ser	Leu	Val	Thr 15	Ile
	Ile	Gly	Asn	Ile 20	Leu	Val	Met	Val	Ser 25	Ile	Lys	Val	Asn	Arg 30	His	Туг
	Phe	Leu	Phe 35	Ser	Ile	Ala	Cys	Ala 40	Asp	Leu	Ile	Ile	Gly 45	Val	Phe	Ser
10	Met	Asn 50	Leu	Tyr	Thr	Leu	Tyr 55	Thr	Val	Ile	Gly	Tyr 60	Trp	Pro	Leu	Gly
	Pro 65	Val	Val	Cys	Asp	Leu 70	Tyr	Val	Val	Ser	Asn 75	Ala	Ser	Val	Met	Asn 80
15	Leu	Leu	Ile	Ile	Ser 85	Phe	qaA	Arg	Tyr	Phe 90	Cys	Val	Thr	Lys	Pro 95	Leu
	Thr	Tyr	Pro	Val 100	Lys	Arg	Thr	Thr	Lys 105	Met	Ala	Gly	Met	Met 110	Ile	Ala
	Ala	Ala	Trp 115	Val	Leu	Ser	Phe	Ile 120	Leu	Trp	Ala	Pro	Ala 125	Ile	Leu	Phe
20	Trp	Gln 130	Phe	Ile	Val	Gly	Val 135	Arg	Thr	Val	Glu	Asp 140	Gly	Glu	Cys	Tyr
	Ile 145	Gln	Phe	Phe	Ser	<b>А</b> вп 150	Pro	Ala	Val	Thr	Phe 155	Gly	Thr	Ala	Ile	Ala 160
25	Ala	Phe	Tyr	Leu	Pro 165	Val	Ile	Ile	Met	Ile 170	Val	Leu	Tyr	Trp	His 175	Ile
	Ser	Arg	Ala	Ser 180	Lys	Ser	Arg	Ile	Lys 185	Lys	Asp	Lys	Lys	Glu 190	Pro	Val
	Ala	Asn	Gln 195	qaA	Pro	Val	Ser	Pro 200	Ser	Leu	Val	Gln	Gly 205	Arg	Ile	Val
30	Lys	Pro 210	Leu	Ser	Ser	qaA	<b>As</b> p 215	Lys	Ile	Val	Arg	Arg 220	Thr	Lys	Gln	Pro
	Ala 225	Lys	Lys	Lys	Pro	Pro 230	Pro	Ser	Arg	Glu	Lys 235	Lys	Val	Thr	Arg	Thr 240
35	Ile	Ala	Ile	Leu	Leu 245	Ala	Phe	Ile	Ile	Thr 250	Trp	Ala	Pro	Tyr	Asn 255	Val
	Met	Val	Leu	11e 260	naA	Thr	Phe	Cys	Ala 265	Pro	Cys	Ile	Pro	Asn 270	Thr	Val
	Trp	Arg	11e 275	Gly	Tyr	Trp	Leu	Cys 280	Tyr	Ile	Asn	Ser	Thr 285	Ile	Asn	Pro
<b>4</b> 0	Ala	Cys 290	Tyr	Ala	Leu	Cys	Asn 295	Ala	Thr	Phe	Lys	Lys 300	Thr	Phe	Lys	His
	Leu 305	Ile	Met	Cys	His	Tyr 310	Lys	Asn	Ile	Gly	Ala 315	Thr	Arg			

(2) INFORMATION FOR SEQ ID NO:11:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 355 amino acids

(B) TYPE: amino acid

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	(ii)	(D)	STI TOI SCULI	POLO	3Y: 3	linea	ar	le								
5	(xi) Trp 1	SEQU Phe	JENCI Ile								Ala	Leu	Val	Thr	Ile 15	Ile
	Gly	Asn	Ile	Leu 20	Val	Ile	Val	Ser	Phe 25	Lys	Val	Asn	Lys	Gln 30	Leu	Lys
10	Thr	Val	Asn 35	naA	Tyr	Phe	Leu	Leu 40	Ser	Leu	Ala	Cys	Ala 45	Asp	Leu	Ile
	Ile	Gly 50	Val	Ile	Ser	Met	Asn 55	Leu	Phe	Thr	Thr	Tyr 60	Ile	Ile	Met	Asr
15	Arg 65	Trp	Ala	Leu	Gly	Asn 70	Thr	Ala	Сув	Asp	Leu 75	Trp	Ile	Ala	Ile	Asp 08
	Tyr	Val	Ala	Ser	Asn 85	Ala	Ser	Val	Leu	Asn 90	Leu	Leu	Val	Ile	Ser 95	Phe
	Asp	Arg	Tyr	Phe 100	Ser	Ile	Thr	Arg	Pro 105	Leu	Thr	Tyr	Arg	Ala 110	Lys	Arg
20	Thr	Thr	<b>Lys</b> 115	Arg	Ala	Gly	Val	<b>M</b> et 120	Ile	Gly	Leu	Ala	Trp 125	Va≟	Ile	Ser
	Phe	<b>Val</b> 130	Leu	Trp	Ala	Pro	Ala 135	Ile	Leu	Phe	Trp	Gln 140	Tyr	Phe	Val	Gly
25	Lys 145	Arg	Thr	Val	Pro	Pro 150	Gly	Glu	Сув	Phe	Ile 155	Gln	Phe	Leu	Ser	Gl: 160
	Pro	Thr	Ile	Thr	Phe 165	Gly	Thr	Ala	Ile	Ala 170	Ala	Phe	Tyr	Met	Pro 175	Va]
	Thr	Ile	Met	Arg 180	Ile	Leu	Tyr	Trp	Arg 185	Ile	Tyr	Lys	Glu	Thr 190	Glu	Lys
30	Arg	Thr	Lys 195	Glu	Leu	Ala	Gly	Leu 200	Gln	Ala	Ser	Gly	Thr 205	Glu	Ala	Gli
	Thr	Glu 210	Asn	Phe	Val	His	Pro 215	Thr	Gly	Ser	Ser	Arg 220	Ser	Суя	Ser	Ser
35	Tyr 225	Glu	Leu	Gln	Gln	Gln 230	Lys	Arg	Phe	Ala	Leu 235	Lys	Thr	Arg	Ser	Glr 240
	Ile	Thr	Lys	Arg	Lys 245	Leu	Leu	Val	Lys	Glu 250	Lys	Lys	Ala	Ala	Gln 255	The
	Leu	Ser	Ala	Ile 260	Leu	Leu	Ala	Phe	11e 265	Ile	Thr	Trp	Thr	Pro 270	Tyr	Asr
40	Ile	Met	Val 275	Leu	Val	Asn	Thr	Phe 280	Cys	qaA	Ser	Сув	Ile 285	Pro	Lys	Thi
	Tyr	Trp 290	Asn	Leu	Gly	Gly	Tyr 295	Trp	Leu	Cys	Tyr	Ile 300	Asn	Ser	Thr	Va]
45	Asn 305	Pro	Val	Cys	Tyr	Ala 310	Leu	Cys	Asn	Lys	Thr 315	Phe	Arg	Thr	Thr	Phe 320
	Lvs	Thr	Leu	Leu	Leu	Cvs	Gln	Cvs	Asp	Lvs	Arg	Lvs	Ara	Ara	Lvs	Glr

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						325					330					335	
		Gln	Tyr	Gln	Gln 340	Arg	Gln	Ser	Val	Ile 345	Phe	His	Lys	Arg	Val 350	Pro	Glu
5		Gln	Ala	Leu 355													
10	(2)	INFOI (i)	SEQU (A) (B) (C) (D)	JENCI LEI TYI STI	CHI NGTH: PE: a RANDI POLOC	ARACT 333 mino EDNES SY: ]	reris ami aci ss: s linea	STICS ino a id sing! ar	S: acids	3							
15		(xi)	SEQU		E DES	CRI	- PTION	N: SI	_			Leu	Ser	Leu	Val	Thr 15	Val
		Val	Gly	Asn	Ile 20	Leu	Val	Met	Leu	Ser 25	Ile	Lys	Val	Asn	Arg 30	Gln	Leu
		Gln	Thr	Val 35	Asn	Asn	Tyr	Phe	Leu 40	Phe	Ser	Ile	Ala	Cys 45	Ala	Asp	Leu
20		Ile	Ile 50	Gly	Ala	Phe	Ser	<b>Me</b> t 55	Asn	Leu	Tyr	Thr	Val 60	Tyr	Ile	Ile	Lys
		Gly 65	Tyr	Trp	Pro	Leu	Gly 70	Ala	Trp	Сув	Asp	Leu 75	Trp	Leu	Ala	Leu	<b>QaA</b> 08
25		Tyr	Val	Val	Ser	Asn 85	Ala	Ser	Val	Met	Leu 90	Leu	Ile	Ile	Ser	Phe 95	Asp
		Arg	Tyr	Phe	Сув 100	Val	Thir	Lys	Pro	Leu 105	Thr	Tyr	Pro	Ala	Arg 111	Arg	Thr
		Thr	Lys	<b>Met</b> 115	Ala	Gly	Ile	Met	Ile 120	Ala	Ala	Ala	Trp	Val 125	Leu	Ser	Phe
30		Val	Leu 130	Trp	Ala	Pro	Ala	Ile 135	Leu	Phe	Trp	Gln	Phe 140	Val	Val	Gly	Lys
		Arg 145	Thr	Val	Pro	Asp	Asn 150	Gln	Cys	Phe	Ile	Gln 155	Phe	Leu	Ser	Asn	Pro 160
35		Ala	Val	Thr	Phe	Gly 165	Thr	Ala	Ile	Ala	Ala 170	Phe	Tyr	Leu	Pro	Val 175	Val
		Ile	Met	Ile	Val 180	Leu	Tyr	Ile	His	Ile 185	Ser	Leu	Ala	Ser	Arg 190	Ser	Arg
		Val	His	Lys 195	His	Arg	Pro	Glu	Gly 200	Pro	Lys	Glu	Lys	Lys 205	Ala	Lys	Thr
40		Ile	Ala 210	Phe	Leu	Lys	Ser	Pro 215		Met	Gln	Ser	Val 220	Lys	Lys	Pro	Pro
		Pro 225	Gly	Glu	Ala	Lys	Phe 230	Ala	Ser	Ile	Ala	Arg 235	Asn	Gln	Val	Arg	Lys 240
<b>4</b> 5		Lys	Arg	Gln	Leu	Ala 245	Ala	Arg	Glu	Arg	Lys 250	Val	Thr	Arg	Thr	Ile 255	Phe
		Ala	Ile	Leu	Leu 260	Ala	Phe	Ile	Leu	Thr 265	Trp	Thr	Pro	Tyr	Asn 270	Val	Met

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		Val	Leu	Val 275	Asn	Thr	Phe	Cys	Gln 280	Ser	Cys	Ile	Pro	Asp 285	Thr	Val	Trp
		Ser	Ile 290	Gly	Tyr	Trp	Leu	Ile 295	Cys	Tyr	Val	Asn	Ser 300	Thr	Ile	Asn	Pro
5		Ala 305	Cys	Tyr	Ala	Leu	Сув 310	Asn	Ala	Thr	Phe	Lys 315	Lys	Thr	Phe	Arg	His 320
		Leu	Leu	Leu	Сув	Gln 325	Arg	Tyr	Asn	Ile	Gly 330	Thr	Ala	Arg			
10	(2)	INFOR	SEQUAL (A)	JENCI LEI TYI STI	E CHI NGTH: PE: & RANDI	ARACT 348 mino SDNES	TERIS Bami Baci BS: 8	STICS ino a id singl	S: acids	5							
15		(ii)				3Y: 1 PE: p											
		(xi) Val 1				CRII Ala 5						Val	Ser	Leu	Met	Thr 15	Ile
20		Val	Gly	Asn	Val 20	Leu	Val	Met	Ile	Ser 25	Phe	Lys	Val	Asn	Ser 30	Gln	Leu
		Lув	Thr	Val 35	Asn	Asn	Tyr	Tyr	Leu 40	Leu	Ser	Ile	Ala	Cys 45	Ala	Asp	Leu
		Ile	Ile 50	Gly	Ile	Phe	Ser	Met 55	Asn	Leu	Tyr	Thr	Thr 60	Tyr	Ile	Leu	Ile
25		<b>M</b> et 65	Gly	Arg	Trp	Ala	Leu 70	Gly	Ser	Leu	Ala	Cys 75	Asp	Leu	Trp	Leu	Ala 80
		Ile	Asp	Tyr	Val	Ala 85	Ser	Asn	Ala	Ser	Val 90	Leu	Asn	Leu	Leu	Val 95	Ile
30		Ser	Phe	Asp	Arg 100	Тух	Phe	Ser	Ile	Thr 105	Arg	Pro	Leu	Thr	Tyr 110	Arg	Ala
		Lys	Arg	Thr 115	Pro	Lys	Arg	Ala	Gly 120	Ile	Met	Ile	Gly	Ile 125	Ala	Trp	Leu
		Ile	Ser 130	Phe	Ile	Leu	Trp	Ala 135	Pro	Ala	Ile	Leu	Cys 140	Trp	Gln	Tyr	Leu
35		Val 145	Gly	Lys	Arg	Thr	Val 150	Pro	Ile	Asp	Glu	Cys 155	Gln	Ile	Gln	Phe	Leu 160
		Ser	Glu	Pro	Thr	Ile 165	Thr	Phe	Gly	Thr	Ala 170	Ile	Ala	Ala	Phe	Tyr 175	Ile
40		Pro	Val	Ser	Ile 180	Met	Arg	Ile	Leu	Tyr 185	Cys	Arg	Ile	Tyr	Arg 190	Glu	Thr
		Glu	Lys	Arg 195	Thr	Lys	Asp	Leu	Ala 200	Asp	Leu	Gln	Gly	Ser 205	Asp	Ser	Val
		Tyr	Lys 210	Ala	Glu	Lys	Arg	<b>Lys</b> 215	Pro	Ala	His	Arg	Ala 220	Leu	Phe	Arg	Ser
45		Cys 225	Leu	Arg	Cys	Pro	Arg 230	Pro	Thr	Lys	Gly	Leu 235	Asn	Pro	Asn	Pro	Ser 240
		His	Gln	Met	Thr	Ινs	Arq	Lys	Arg	Met	Ser	Leu	Val	Lys	Glu	Arg	Lys

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						245					250					255	
		Ala	Ala	Gln	Thr 260	Leu	Ser	Ala	Ile	Leu 265	Leu	Ala	Phe	Ile	11e 270	Thr	Trp
5		Thr	Pro	Tyr 275	Asn	Ile	Met	Val	Leu 280	Val	Ser	Thr	Phe	Cys 285	Asp	Lys	Cys
		Val	Pro 290	Val	Thr	Leu	Trp	His 295	Leu	Gly	Tyr	Trp	Leu 300	Cys	Tyr	Ile	Asn
		Ser 305	Thr	Val	Asn	Pro	Ile 310	Cys	Tyr	Ala	Leu	Cys 315	Asn	Arg	Thr	Phe	Arg 320
10		Lys	Thr	Phe	Ile	Met 325	Leu	Leu	аүЭ	Arg	Trp 330	Lys	Lys	Lys	Lys	Val 335	Glu
		Glu	Lys	Leu	Tyr 340	Trp	Gln	Gly	Asn	Ser 345	Lys	Leu	Pro				
15	(2)		SEQI (A (B (C	ION I UENCI ) LEI ) TYI ) STI ) TOI	E CHA NGTH: PE: & RANDE	ARACT 377 mino EDNES	TERIS 7 aum: 5 ac: 5S: 8	STICS ino a id sing!	S: acids	5							
20		(ii)		ECULI													
		(xi) Thr 1	SEQ: Ala	Gly	Asp	Cys 5	PTIO Leu	N: SI Ile	EQ II <b>M</b> et	Leu	:14: Ile 10	Val	Leu	Leu	Ile	Val 15	Ala
25		Gly	Asn	Val	Leu 20	Val	Ile	Val	Ala	Ile 25	Ala	Lys	Thr	Pro	Arg 30	Leu	Gln
		Thr	Leu	Thr 35	Asn	Leu	Phe	Ile	<b>M</b> et <b>4</b> 0	Ser	Ile	Ala	Ser	Ala 45	qaA	Leu	Val
		Met	Leu 50	Leu	Leu	Val	Val	Pro 55	Phe	Суѕ	Ala	Thr	Leu 60	Val	Val	Trp	Gly
30		Arg 65	Trp	Glu	Tyr	Gly	Ser 70	Phe	Phe	Cys	Glu	Leu 75	Trp	Thr	Ser	Val	Asp 80
		Val	Leu	сув	Val	Thr 85	Ala	Ser	Ile	Glu	Thr 90	Leu	Cys	Val	Ile	Ala 95	Leu
35					100					105		Arg			110		
				115					120	l				125			Ser
			130	)				135					140				Arg
40		145	į				150	)				155					Tyr 160
						165	i				170	)				175	
45		Phe	· Val	Туг	Leu 180		Val	Phe	Arg	Gli 185	ı Ala	a Glm	Lys	Glr	190	Lys	Lys
		Il€	Ası	Ser 195		Glu	ı Arg	g Arg	200		ı Gly	/ Gly	Pro	205	a Arg	Pro	Pro

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	Se	Pro 210		Pro	Ser	Pro	Val 215	Pro	Ala	Pro	Ala	Pro 220	Pro	Gly	Pro	Pro
	Arc 22	g Pro	Ala	Ala	Ala	Ala 230	Ala	Thr	Ala	Pro	Leu 235	Ala	Asn	Gly	Arg	Ala 240
5	Gl	/ Lys	Arg	Arg	Pro 245	Ser	Arg	Leu	Val	Ala 250	Leu	Arg	Glu	Gln	Lys 255	Ala
	Lev	ı Lys	Thr	Leu 260	Gly	Ile	Ile	Met	Gly 265	Val	Phe	Thr	Leu	Cys 270	Trp	Leu
10	Pro	) Phe	Phe 275	His	Arg	Glu	Leu	Val 280	Pro	Asp	Arg	Leu	Phe 285	Val	Phe	Phe
	Ası	1 Trp 290		Arg	Tyr	Ala	Asn 295	Ser	Ala	Phe	Asn	Pro 300	Ile	Ile	Tyr	Cys
	Arg 305	Ser	Pro	qaA	Phe	<b>A</b> rg 310	Lys	Ala	Phe	Gln	Gly 315	Leu	Leu	Cys	Сув	Ala 320
15	Arg	J Arg	Ala	Ala	Arg 325	Arg	Arg	His	Ala	Thr 330	His	Gly	Asp	Arg	Pro 335	Arg
	Ala	a Ser	Gly	Cys 340	Ile	Ala	Arg	Pro	Gly 3 <b>4</b> 5	Pro	Pro	Ser	Pro	Gly 350	Ala	Ala
20	Sea	qaA	<b>Asp</b> 355	qaA	Asp	qaA	дар	Val 360	Val	Gly	Ala	Thr	Pro 365	Pro	Ala	Arg
	Let	1 Leu 370	Glu	Pro	Trp	Ala	Gly 375	Сув	Asn							
		RMAT SEQ														
25		(A (B (C	) LEI ) TYI ) STI ) TOI	NGTH PE: & RANDI POLO	: 362 amino EDNES GY: ]	2 ami 5 aci 5S: s linea	ino a id sing: ar	acida	5							
25 30	(ii) (xi)	(A (B (C (D	) LEI ) TYI ) STI ) TOI ECULI UENCI	NGTH PE: 6 RANDI POLO E TYI E DES	: 362 amino EDNES GY: 1 PE: p	2 ami 5 aci 5S: s linea pepti PTIO	ino a id sing: ar ide N: SI	acida le EQ II	O NO:		Leu	Ala	Ile	Val	Phe 15	Gly
	(ii) (xi) Val 1	(A (B (C (D MOL SEQ	) LEI ) TYI ) STI ) TOI ECULI UENCI Gly	NGTH PE: 6 RANDI POLOG E TYI E DES	: 362 amino EDNES GY: 1 PE: p ECRII Val	2 ami 5 aci 5S: s linea pepti PTION Met	ino a id sing: ar ide N: SI Ser	acids le EQ II Leu	NO: Ile	Val 10					15	-
	(ii) (xi) Val 1 Asr	(A (B (C (D MOL SEQ Val	) LEI ) TYI ) STI ) TOI ECULI UENCI Gly Leu	NGTH PE: & RANDI POLOG E TYI E DES Ile Val 20	: 362 amino EDNES GY: 1 PE: p SCRIN Val 5	2 amico aciones: ss: stines open times open	ino a id sing: ar ide V: SI Ser	acids le EQ II Leu Ile	NO: Ile Ala 25	Val 10 Lys	Phe	Glu	Arg	Leu 30	15 Gln	Thr
30	(ii) (xi) Val Asr Val	(A (B (C (D MOL SEQ Val	) LEI ) TYI ) STI ) TOI ECULI UENCI Gly Leu Asn 35	NGTH PE: a RANDI POLOO E TYI E DES Ile Val 20 Tyr	: 362 amino EDNES GY: 1 PE: 1 CCRII Val 5 Ile Phe	2 amico aciones services servi	ino aid sing: ar ide N: SI Ser Ala	e EQ II Leu Ile Ser	NO: Ile Ala 25 Ile	Val 10 Lys Ala	Phe Cys	Glu Ala	Arg Asp 45	Leu 30 Leu	15 Gln Val	Thr Met
30	(ii) (xi) Val 1 Ass Val	(A (B (C (D MOL SEQ Val	) LEI ) TYI ) STI ) TOI ECULI UENCI Gly Leu Asn 35	Val Val Val Val	: 362 amino EDNES GY: 1 PE: 1 SCRIN Val  Phe Val	2 amporton acception acceptance acception acceptance acceptanc	ino aid sing: ar ide N: SI Ser Ala Thr	EQ II Leu Ile Ser 40	O NO: Ile Ala 25 Ile Ala	Val 10 Lys Ala Ala	Phe Cys His	Glu Ala Ile 60	Arg Asp 45 Leu	Leu 30 Leu Met	15 Gln Val Lys	Thr Met
30	(ii) (xi) Val  Asr  Val  Gly  Trg 65	(A (B (C) (D MOL SEQ Val Val Thr	) LEI ) TYI ) STI ) TOI ECULI UENCI Gly Leu Asn 35 Ala	NGTH PE: a RANDI POLOO E TYI E DES Ile Val 20 Tyr Val Gly	: 362 amino EDNES GY: 1 PE: 1 SCRIM Val Ile Phe Val Asn	2 amporton acress: string acress string acres acres string acres acres acres string acres acres string acres acres string acres	ino aid sing: ar ide N: SI Ser Ala Thr Phe 55	EQ II Leu Ile Ser 40 Gly	NO: Ile Ala 25 Ile Ala Glu	Val 10 Lys Ala Ala Phe	Phe Cys His Trp 75	Glu Ala Ile 60 Thr	Arg Asp 45 Leu Ser	Leu 30 Leu Met	15 Gln Val Lys Asp	Thr Met Met Val
30	(ii) (xi) Val  Ass  Val  Gly  Trg 65	(A (B (C) (D) MOL SEQ Val Val Thr	) LEI ) TYI ) STI ) TOI ECULI UENCI Gly Leu Asn 35 Ala Phe Val	Val Coly	: 362 amino EDNES GY: 1 PE: P SCRII Val 5 Ile Phe Val Asn Ala 85	2 amborace acception of the company	ino aid sing: ar ide Ser Ala Thr Phe 55 Trp	EQ II Leu Ile Ser 40 Gly Cys	Ala 25 Ile Ala Glu	Val 10 Lys Ala Ala Phe Leu 90	Phe Cys His Trp 75 Cys	Glu Ala Ile 60 Thr	Arg Asp 45 Leu Ser	Leu 30 Leu Met Ile	15 Gln Val Lys Asp Val 95	Thr Met Met Val 80 Asp
30	(ii) (xi) Val  Ass Val  Gly Trg 65 Let	(A (B (C (D MOL SEQ Val Val Thr Leu 50 Thr	) LEI ) TYI ) STI ) TOI ECULI UENCI Gly Leu Asn 35 Ala Phe Val	Val Gly Thr	: 362 amino EDNES GY: 1 PE: I SCRII 5 Ile Phe Val Asn Ala 85 Ile	2 ample access: strings series and series access series ac	ino aid sing ide	EQ II Leu Ile Ser 40 Gly Cys Glu Pro	O NO: Ile Ala 25 Ile Ala Glu Thr	Val 10 Lys Ala Ala Phe Leu 90 Lys	Phe Cys His Trp 75 Cys	Glu Ala Ile 60 Thr Val	Arg Asp 45 Leu Ser Ile	Leu 30 Leu Met Ile Ala Leu 110	Gln Val Lys Asp Val 95 Leu	Thr Met Met Val 80 Asp

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			130					135					140				
		Ile 145	Asn	Cys	Tyr	Ala	Asn 150	Glu	Thr	Cys	Cys	<b>As</b> p 155	Phe	Phe	Thr	Asn	Gln 160
5		Ala	Tyr	Ala	Ala	Ser 165	Ser	Ala	Val	Ser	Phe 170	Tyr	Val	Pro	Leu	Val 175	Ile
		Met	Val	Phe	Val 180	Tyr	Ser	Arg	Val	Phe 185	Gln	Glu	Ala	Lys	Arg 190	Gln	Leu
		Gln	Lys	Ile 195	qaA	Lys	Ser	Glu	Gly 200	Arg	Phe	Ile	Phe	Val 205	Gln	Asn	Leu
10		Ser	Gln 210	Val	Glu	Gln	Asp	Gly 215	Arg	Thr	Gly	His	Gly 220	Leu	Arg	Arg	Ser
		Ser 225	Lys	Phe	Cys	Leu	Lys 230	Glu	His	Lys	Ala	Leu 235	Lys	Thr	Leu	Gly	Ile 240
15		Ile	Pro	Cys	Thr	Phe 245	Thr	Leu	Cys	Trp	Leu 250	Pro	Phe	Phe	Ile	Val 255	Asn
		Ile	Val	Val	Ile 260	Gln	Asp	Asn	Leu	Ile 265	Arg	Lys	Glu	Val	Tyr 270	Ile	Leu
	•	Leu	Asn	Trp 275	Ile	Gly	Tyr	Val	Asn 280	Ser	Gly	Phe	Asn	Pro 285	Leu	Ile	Tyr
20		Cys	Arg 290	Ser	Pro	Asp	Phe	Arg 295	Ile	Ala	Phe	Gln	Glu 300	Leu	Leu	Cys	Leu
		Arg 305	Arg	Ser	Ser	Leu	Lys 310	Ala	Tyr	Gly	Asn	Gly 315	Tyr	Ser	Ser	Asn	Gly 320
25		Asn	Thr	Gly	Glu	Gln 325	Ser	Gly	Tyr	His	Val 330	Glu	Gln	Glu	Lys	Glu 335	Asn
		Lys	Leu	Leu	Cys 340	Glu	Asp	Leu	Pro	Gly 3 <b>4</b> 5	Thr	Glu	Asp	Phe	Val 350	Gly	His
		Gln	Gly	Thr 355	Val	Pro	Ser	Asp	Asn 360	Ile	qaA						
30	(2)	INFOI (i)	SEQUAL (A)	ION I JENCI LEI TYI	CHA TGTH: PE: 8	ARACT : 362 amino	TERIS 2 ami 3 ac:	STICS ino a id	S: acida	5							
35		(ii)	(D)	TOI	OTO	3Y: 3	linea	ar									
		(xi) Ala 1		JENCI Leu								Ala	Val	Leu	Ala	Thr 15	Val
40		Gly	Gly	Asn	Leu 20	Leu	Val	Ile	Val	Ala 25	Ile	Ala	Trp	Thr	Pro 30	Arg	Leu
		Gln	Thr	<b>M</b> et 35	Thr	Asn	Val	Phe	Val 40	Thr	Ser	Leu	Ala	Ala 45	Ala	Asp	Leu
<b>4</b> 5		qaA	Leu 50	Leu	Val	Val	Pro	Pro 55	Ala	Ala	Thr	Leu	Ala 60	Leu	Thr	Gly	His
		Trp 65	Pro	Leu	Gly	Ala	Thr 70	Gly	Сув	Glu	Leu	Trp 75	Thr	Ser	Val	Asp	Val 80

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		Leu	Сув	Val	Thr	Ala 85	Ser	Ile	Glu	Thr	Leu 90	Cys	Ala	Ile	Ala	Val 95	Asp
		Arg	Tyr	Leu	Ala 100	Val	Thr	Asn	Pro	Leu 105	Arg	Tyr	Gly	Ala	Leu 110	Val	Thr
5		Lys	Arg	Cys 115	Ala	Arg	Thr	Ala	Trp 120	Leu	Val	Trp	Val	<b>Val</b> 125	Ser	Ala	Ala
		Val	Ser 130	Phe	Ala	Pro	Ile	Met 135	Ser	Gln	Trp	Trp	Arg 140	Val	Gly	Ala	Asp
LO		Ala 145	Glu	Ala	Gln	Arg	Cys 150	His	Ser	Asn	Pro	Arg 155	Cys	Сув	Ala	Phe	Ala 160
		Ser	Asn	Met	Pro	Tyr 165	Ala	Val	Leu	Leu	Ser 170	Ser	Ser	Val	Ser	Phe 175	Tyr
		Leu	Pro	Leu	Leu 180	Leu	Phe	Val	Tyr	Ala 185	Arg	Val	Phe	Trp	Ala 190	Thr	Arg
15		Gln	Leu	Arg 195	Leu	Leu	Arg	Gly	Glu 200	Leu	Gly	Arg	Phe	Pro 205	Pro	Glu	Glu
		Ser	Pro 210	Pro	Ala	Pro	Ser	Arg 215	Ser	Leu	Ala	Pro	Ala 220	Pro	Val	Gly	Thr
20		Gly 225	Ala	Pro	Pro	Glu	Gly 230	Val	Pro	Ala	Cys	Gly 235	Arg	Pro	Pro	Ala	Arg 240
		Leu	Ile	Pro	Ile	Arg 245	Glu	His	Arg	Ala	Leu 250	Сув	Thr	Leu	Gly	<b>Leu</b> 255	Ile
		Met	Gly	Thr	Phe 260	Thr	Leu	Cys	Trp	Leu 265	Pro	Phe	Phe	Ile	Ala 270	Asn	Val
25		Leu	Arg	Ala 275	Leu	Gly	Gly	Pro	Ser 280	Leu	Val	Pro	Gly	Pro 285	Ala	Phe	Leu
		Ala	Leu 290		Trp	Leu	Ile	Gly 295	Tyr	Ala	Asn	Ser	Ala 300	Phe	Asn	Pro	Leu
30		Ile 305		Cys	Arg	Ser	Pro 310		Phe	Arg	Ser	Ala 315	Phe	Arg	Arg	Leu	<b>Leu</b> 320
		Cys	Arg	Cys	Gly	Arg 325	Arg	Leu	Pro	Pro	Glu 330	Pro	Сув	Ala	Ala	Ala 335	Arg
		Pro	Ala	Leu	Phe 340	Pro	Ser	Gly	Val	Pro 345	Ala	Ala	Glu	Ser	Ser 350	Pro	Ala
35		Gln	Pro	Arg 355		Суѕ	Gln	Arg	Leu 360		Gly	•					
40	2)		SEQ (A (B	UENC UENC ) LE ) TY ) ST	E CH NGTH PE: RAND	ARAC : 37 amin EDNE	TERI 5 am 10 ac SS:	STIC ino id sing	S: acid	ls							
			MOI	ECUL	E TY	PE:	pept	ide									
45		(xi) Ala 1	SEC 11e	UENC Leu	E DE Leu	SCRI Gly 5	PTIC Val	N: S . Ile	EQ I Leu	D NO	0:17: / Gly 10	Leu	ılle	e Lev	Phe	Gly 15	Val
		Lev	ı Gla	Asn	ılle	Lev	ı Val	Ile	Leu	Ser	. Val	Ala	а Суз	His	Arg	His	Leu

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				20					25					30		
	His	Ser	Val 35	Thr	His	Tyr	Tyr	Ile 40	Val	naA	Leu	Ala	Val 45	Ala	Asp	Leu
5	Leu	<b>Leu</b> 50	Thr	Ser	Thr	Val	Leu 55	Pro	Phe	Ser	Ala	Ile 60	Phe	Glu	Ile	Leu
	Gly 65	Tyr	Trp	Lys	Phe	Gly 70	Arg	Val	Phe	Cys	Asn 75	Val	Trp	Ala	Ala	Val 80
	qaA	Val	Leu	Сув	Cys 85	Thr	Ala	Ser	Ile	<b>M</b> et 90	Leu	Leu	Cys	Ile	Ile 95	Ser
10.				100		Gly			105					110		
			115			Gly		120					125			
15		130				Ile	135					140				
	145					Ile 150					155					160
					165	Gly				170					175	
20			_	180		Val			185					19"		
			195			Lys		200					205			
25		210		•		Lys 	215	1				220				
	225					Thr 230					235					240
2.0					245					250					255	
30				260		Pro			265					270		
			275			Pro		280					285			
35		290				Ser	295					300				
	305					10 310					315					320
					325					330					335	
40				340		Leu			345					350	1	
			355			Glu		360		Lys	: Ile	s Ser	365		Asp	Gly
45	Val	Cys 370		Trp	Lys	: Ile	Phe 375									

5	(2)	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 370 amino acids  (B) TYPE: amino acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: peptide															
10		(xi) Ala 1	SEQU Ile	ENCE Ser	DES Val	CRIP Gly 5	TION Leu	: SE Val	Q ID Leu	NO: Gly	18: Ala 10	Phe	Ile	Leu	Phe	Ala 15	Ile
		Val	Gly	Asn	Ile 20	Leu	Val	Ile	Leu	Ser 25	Val	Ala	Cys	Asn	Arg 30	His	Leu
- 30-		Arg	Thr	Pro 35	Thr	Asn	Tyr	Phe	Ile 40	Val	Asn	Ile	Ala	Ile 45	Ala	Asp	Leu
15		Leu	Leu 50	Ser	Phe	Thr	Val	Leu 55	Pro	Phe	Ser	Ala	Thr 60	Leu	Glu	Val	Leu
		Gly 65	Tyr	Trp	Val	Leu	Gly 70	Arg	Ile	Phe	Cys	<b>Asp</b> 75	Ile	Trp	Ala	Ala	Val 80
20		qaA	Val	Leu	Сув	Суs 85	Thr	Ala	Ser	Ile	Leu 90	Ser	Leu	Cys	Ala	Ile 95	Ser
		Ile	Asp	Arg	Tyr 100	Ile	Gly	Val	Arg	Tyr 105	Ser	Leu	Gln	Tyr	Pro 110	Thr	Leu
		Val	Thr	Arg 115	Arg	Tyr	Ala	Ile	Ile 120	Ala	Leu	Leu	Ser	Val 125	Trp	Val	Leu
25		Ser	Thr 130	Val	Ile	Ser	Ile	Gly 135	Pro	Leu	Leu	Gly	Trp 140	Lys	Glu	Pro	Ala
		Pro 145	Asn	Asp	qaA	Lys	Glu 150	Cys	Val	Thr	Glu	Glu 155	Pro	Phe	Leu	Phe	Суs 160
30		Ser	Leu	Gly	Ser	Phe 165	Tyr	Ile	Pro	Ile	Ala 170	Val	Ile	Leu	Val	<b>M</b> et 175	Tyr
		Суѕ	Arg	Val	Tyr 180	Ile	Val	Ala	Lys	<b>Arg</b> 185	Thr	Thr	Lys	Asn	Leu 190	Glu	Ala
		Gly	Val	<b>M</b> et 195		Glu	Met	Ser	Asn 200	Ser	Lys	Phe	Leu	Thr 205	Leu	Arg	Ile
35		His	Trp 210		Lys	naA	Phe	His 215	Glu	Asp	Thr	Leu	Ser 220	Ser	Thr	Lys	Ala
		<b>Lys</b> 225	Gly	His	Asn	Pro	<b>A</b> rg 230		Ser	Ile	Ala	Val 235	Lys	Leu	Phe	Lys	Phe 240
40		Ser	Arg	Glu	Lys	Lys 245		Ala	Lys	Thr	Leu 250	Gly	Ile	Val	Val	Gly 255	Trp
		Ile	Leu	Cys	Trp 260		Pro	Phe	Phe	Ile 265	Ala	Leu	Pro	Leu	Gly 270	Ser	Leu
		Phe	Ser	Thr 275		Lys	Pro	Pro	Asp 280		Val	Phe	Lys	285	Phe	Trp	Leu
45		Gly	Tyr 290		. Asn	. Ser	Cys	Leu 295	Asn	Pro	) Ile	Ile	Tyr 300	Pro	Cys	Ser	Ser
		Lys	Glu	. Phe	Lys	Arg	Ala	Leu	Leu	Gly	cys	Gln	Сув	Arg	g Gly	r Gly	Arg

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		305					310					315					320
		Arg	Arg	Arg	Arg	<b>Ar</b> g 325	Arg	Arg	Leu	Ala	Cys 330	Ala	Tyr	Thr	Tyr	<b>Ar</b> g 335	Pro
5		Trp	Thr	Arg	Gly 340	Gly	Ser	Leu	Glu	Arg 345	Ser	Gln	Ser	Arg	Lys 350	Asp	Ser
		Ile	qzA	Asp 355	Ser	Gly	Ser	Cys	Met 360	Ser	Gly	Gln	Lys	Arg 365	Thr	Leu	Pro
		Ser	Ala 370														
10 15	(2) I		SEQU (A) (B) (C)	ENCE LEN TYE STE	CHA GTH: PE: a RANDE	RACT 330 mino	ERIS ami aci S: s	ingl	: cids	;							
	(	ii)				E: p											
		Val						I: SE Val			Phe	Leu	Ile	Val	Phe		Val
20		ı Val	Gly	naA	Val 20	5 Leu	Val	Val	Ile	Ala 25	10 Val	Leu	Thr	Ser	Arg 30	15 Ala	Leu
,		Arg	Ala	Pro 35		Asn	Leu	Phe	Leu 40		Ser	Ile	Ala	Ser 45		Asp	Ile
25		Leu	<b>Val</b> 50	Ala	Thr	Leu	Val	<b>Me</b> t 55	Pro	Phe	Ser	Leu	Ala 60	Asn	Glu	Ile	Met
		Tyr 65	Trp	Tyr	Phe	Gly	Gln 70	Val	Trp	Сув	Gly	<b>Val</b> 75	Tyr	Leu	Ala	Ile	Asp 80
		Val	Leu	Phe	Cys	Thr 85	Ser	Ser	Ile	Val	His 90	Leu	Cys	Ala	Ile	Ser 95	Leu
30		Asp	Arg	Tyr	Trp 100	Ser	Val	Thr	Gln	Ala 105	Val	Glu	Tyr	Asn	Leu 110	Lys	Arg
				115			-	Ala	120					125			
35			130					Pro 135					140				
		Gly 145	Ala	Ala	Tyr	Pro	<b>Gl</b> n 150	Cys	Gly	Leu	Asn	<b>As</b> p 155	Glu	Thr	Trp	Tyr	11e 160
		Leu	Ser	Ser	Сув	Ile 165	Gly	Ser	Phe	Phe	Ala 170	Pro	Сув	Leu	Ils	Tyr 175	Leu
40		Leu	Val	Tyr	Ala 180	Arg	Ile	Tyr	Arg	<b>Va</b> l 185	Ala	Lys	Arg	Arg	Thr 190	Arg	Thr
		Leu	Ser	Glu 195	Lys	Arg	Ala	Pro	Val 200	Gly	Pro	qaA	Gly	Ala 205	Ser	Pro	Thr
45		Thr	Glu 210	Asn	Gly	Leu	Gly	Ala 215	Ala	Ala	Gly	Glu	Ala 220	Arg	Thr	Gly	Thr
		Ala 225	Arg	Phe	Leu	Ser	<b>Arg</b> 230	Arg	Arg	Arg	Ala	Arg 235	Ser	Ser	Val	Cys	Arg 240
		Arg	Lys	Val	Ala	Gln	Ala	Arg	Glu	Lys	Arg	Phe	Thr	Phe	Val	Leu	Ala

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						245					250					255	
		Leu	Val	Phe	Val 260	Leu	Cys	Trp	Phe	Pro 265	Phe	Phe	Phe	Ile	Tyr 270	Ser	Leu
5		Tyr	Gly	Ile 275	Cys	Arg	Glu	Ala	Cys 280	Gln	Val	Pro	Gly	Pro 285	Leu	Phe	Lys
		Phe	Phe 290	Phe	Trp	Ile	Gly	Tyr 295	Суѕ	Asn	Ser	Ser	Leu 300	Asn	Pro	Val	Ile
		Tyr 305	Thr	Val	Phe	Asn	Gln 310	qaA	Phe	Arg	Pro	Ser 315	Phe	Lys	His	Ile	Leu 320
10		Phe	Arg	Arg	Arg	Arg 325	Arg	Gly	Phe	Arg	Gln 330						
15	(2)		SEQUAL (A)	JENCI LEI TYI STI	E CHI NGTH PE: 8 RANDI POLO	ARAC : 330 amino EDNE SY:	reris cam: cac: ss: s line	STICS ino a id sing! ar	3: acids	5							
		(xi)	SEQ	JENCI	E DES	SCRII	PTIO	N: SI	EQ II	NO:	:20:						
20		Thr 1	Ala	Ala	Ile	Ala 5	Ala	Ala	Ile	Thr	Phe 10	Leu	Ile	Leu	Phe	Thr 15	Ile
		Phe	Gly	Asn	Ala 20	Leu	Val	Ile	Ile	Ala 25	Val	Leu	Thr	Ser	Arg 30	Ser	Leu
25		Arg	Ala	Pro 35	Gln	Asn	Leu	Phe	Leu 40	Val	Ser	Ile	Ala	Ala 45	Ala	Asp	Ile
		Leu	<b>Val</b> 50	Ala	Thr	Leu	Ile	Ile 55	Pro	Phe	Ser	Leu	Ala 60	Asn	Glu	Leu	Leu
		Gly 65	Tyr	Trp	Tyr	Phe	Arg 70	Arg	Thr	Trp	Cys	Glu 75	Val	Tyr	Leu	Ala	Leu 80
30		Asp	Val	Leu	Phe	Cys 85	Thr	Ser	Ser	Ile	Val 90	His	Leu	Cys	Ala	Ile 95	Ser
		Leu	Asp	Arg	Tyr 100	Trp	Ala	Val	Ser	Arg 105	Ala	Leu	Glu	Tyr	Asn 110	Ser	Lys
35		Arg	Thr	Pro 115	Arg	Arg	Ile	Lys	Cys 120	Ile	Ile	Leu	Thr	Val 125	Trp	Leu	Ile
		Ala	Ala 130	Val	Ile	Ser	Leu	Pro 135	Pro	Leu	Ile	Tyr	Lув 140	Gly	qaA	Gln	Gly
		Pro 145	Gln	Pro	Arg	Gly	Arg 150	Pro	Gln	Cys	Lys	Leu 155	Asn	Gln	Glu	Ala	Trp 160
40		Tyr	Ile	Leu	Ser	Ser 165	Ile	Gly	Ser	Phe	Phe 170	Ala	Pro	Cys	Leu	Ile 175	Leu
		Leu	Val	Tyr	Leu 180	Arg	Ile	Tyr	Leu	Ile 185	Ala	Lys	Arg	Ser	<b>As</b> 11	Arg	Arg
45		Gly	Pro	Arg 195	Ala	rys	Cys	Gly	Pro 200	Gly	Gln	Gly	Glu	Ser 205	Lys	Gln	Pro
		Arg	Pro	Asp	His	Gly	Gly	Ala	Ile	Ala	Ser	Ala	Lys	Leu	Pro	Ala	Ile

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			210					215					220				
		Ala 225	Ser	Gly	Arg	Gly	Val 230	Gly	Ala	Ile	Gly	Gly 235	Gln	Trp	Trp	Arg	Arg 240
5		Arg	Ala	His	Val	Thr 245	Arg	Glu	Lys	Arg	Phe 250	Thr	Phe	Val	Leu	Ala 255	Val
		Val	Ile	Gly	Val 260	Phe	Val	Leu	Cys	Trp 265	Phe	Pro	Phe	Phe	Phe 270	Ser	Tyr
		Ser	Leu	Gly 275	Ala	Ile	Cys	Pro	Lys 280	His	Cys	Lys	Val	Pro 285	His	Gly	Leu
10		Phe	Gln 290	Phe	Phe	Phe	Trp	Ile 295	Gly	тут	Сув	Asn	Ser 300	Ser	Leu	Asn	Pro
		Val 305	Ile	Tyr	Thr	Ile	Phe 310	Asn	Gln	Asp	Phe	Arg 315	Met	Phe	Arg	Arg	11e 320
15		Leu	Сув	Arg	Pro	Trp 325	Thr	Gln	Thr	Ala	Trp 330						
20	(2)	(ii)	SEQU (A) (B) (C) (D)	JENCI LEI TYI STI	CHI NGTH PE: 6 RANDI POLOC	ARACT 330 mino EDNES Y: 1	reris am: ac: ss: s linea	TICS ino a id sing: ar	S: acids	5							
						_	-		TI	. NO	. 23 .						
25		(xi) Thr 1	_						_			Ser	Leu	Thr	Val	Phe 15	Gly
		Asn	Val	Leu	Val 20	Ile	Ile	Ala	Val	Phe 25	Thr	Ser	Arg	Ala	Leu 30	Lys	Ala
		Pro	Gln	Asn 35	Leu	Phe	Leu	Val	Ser 40	Ile	Ala	Ser	Ala	Asp 45	Ile	Leu	Val
30		Ala	Thr 50	Leu	Val	Ile	Pro	Phe 55	Ser	Leu	Ala	Asn	Glu 60	Val	Asn	Gly	Tyr
		Trp 65	Tyr	Phe	Gly	Lys	Trp 70	Cys	Glu	Ile	Tyr	Leu 75	Ala	Leu	Asp	Val	Leu 80
35			-	Thr		85					90					95	
		-	-		100					105	_			_	110		Pro
		_		115	-				120					125			Val
40			130					135					140			_	Gly
		145					150					<b>15</b> 5					Trp 160
45		-		Ile		165					170				_	175	
		Trp	Leu	Val	Tyr 180	Val	Arg	Ile	Tyr	Gln 185	Ile	Ala	Lys	Arg	Arg 190	Thr	Arg

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			PIO	195	ser	Arg	Arg	Asp	200	Asp	Ala	vai	АТА	205	Pro	Pro	Gry
		Gly	Thr 210	Glu	Arg	Arg	Pro	Asn 215	Gly	Leu	Gly	Pro	Glu 220	Arg	Ser	Ala	Gly
5		Pro 225	Gly	Gly	Gly	Arg	Gly 230	Arg	Ser	Ala	Ser	Gly 235	Leu	Pro	Arg	Arg	Arg 240
		Ala	Gly	Ala	Gly	Gly 245	Gln	Asn	Arg	Glu	<b>Lys</b> 250	Arg	Phe	Thr	Phe	Val 255	Ile
LO		Ala	Val	Val	Ile 260	Gly	Val	Phe	Val	Val 265	Cys	Trp	Phe	Pro	Phe 270	Phe	Phe
		Thr	Tyr	Thr 275	Leu	Thr	Ala	Val	Leu 280	Cys	Ser	Val	Pro	Arg 285	Thr	Leu	Phe
		Lys	Phe 290	Phe	Phe	Trp	Phe	Gly 295	Tyr	Сув	Asn	Ser	Ser 300	Leu	Asn	Pro	Val
L5		Ile 305	Tyr	Thr	Ile	Phe	<b>Asn</b> 310	His	Asp	Phe	Arg	<b>Arg</b> 315	Ala	Phe	Lys	Lys	Ile 320
		Leu	Cys	Arg	Gly	Asp 325	Arg	Lys	Arg	Ile	Val 330						
20	(2)	(ii)	SEQU (A) (B) (C) (D)	JENCI LEI TYI STI	CHI NGTH: PE: & RANDI POLOC	ARAC: 334 mino SDNES SY:	reris Lami Saci SS: s Linea	STICS ino a id singl	S: acida	5							
		(xi) Thr 1	SEQU Leu									Ile	Met	Leu	Ph≑	Thr 15	Val
30																	
		Phe	Gly	Asn	<b>Val</b> 20	Leu	Val	Ile	Ile	Ala 25	Val	Phe	Thr	Ser	Arg 30	Ala	Leu
			Gly Ala		20					25					30		
		Lys	_	Pro 35	20 Gln	Asn	Leu	Phe	Leu 40	25 Val	Ser	Ile	Ala	Ser 45	30 Ala	Asp	Ile
35		Lys Leu	Ala Val	Pro 35 Ala	20 Gln Thr	<b>A</b> sn Leu	Leu Val	Phe Ile 55	Leu 40 Pro	25 Val Phe Cys	Ser Ser Glu	Ile Leu	Ala Ala 60 Tyr	Ser 45 Asn	30 Ala Glu	Asp Val	Ile Met
35		Lys Leu Tyr 65	Ala Val 50	Pro 35 Ala Tyr	20 Gln Thr Phe	Asn Leu Gly	Leu Val Lys 70	Phe Ile 55 Val	Leu 40 Pro Trp	25 Val Phe Cys	Ser Ser Glu	Ile Leu Ile 75	Ala Ala 60 Tyr	Ser 45 Asn Leu	30 Ala Glu Ala	Asp Val Ile	Ile Met Asp 80
35 10		Lys Leu Tyr 65 Val	Ala Val 50 Trp	Pro 35 Ala Tyr	20 Gln Thr Phe Cys	Asn Leu Gly Thr	Leu Val Lys 70 Ser	Phe Ile 55 Val Ser	Leu 40 Pro Trp	25 Val Phe Cys Val	Ser Ser Glu His	Ile Leu Ile 75 Leu	Ala Ala 60 Tyr Cys	Ser 45 Asn Leu Ala	30 Ala Glu Ala Ile	Asp Val Ile Ser 95	Met Asp 80
		Lys Leu Tyr 65 Val	Ala Val 50 Trp Leu	Pro 35 Ala Tyr Phe	20 Gln Thr Phe Cys Trp 100	Asn Leu Gly Thr 85 Ser	Leu Val Lys 70 Ser	Phe Ile 55 Val Ser Thr	Leu 40 Pro Trp Ile	25 Val Phe Cys Val Ala 105	Ser Ser Glu His 90	Ile Leu Ile 75 Leu Glu	Ala Ala 60 Tyr Cys	Ser 45 Asn Leu Ala Asn	30 Ala Glu Ala Ile Leu 110	Asp Val Ile Ser 95	Met Asp 80 Leu
		Lys Leu Tyr 65 Val Asp	Ala Val 50 Trp Leu Arg	Pro 35 Ala Tyr Phe Tyr Arg	Gln Thr Phe Cys Trp 100 Arg	Asn Leu Gly Thr 85 Ser	Leu Val Lys 70 Ser Ile Lys	Phe Ile 55 Val Ser Thr	Leu 40 Pro Trp Ile Gln Ile 120	25 Val Phe Cys Val Ala 105 Ile	Ser Ser Glu His 90 Ile Val	Ile Leu Ile 75 Leu Glu	Ala Ala 60 Tyr Cys Tyr	Ser 45 Asn Leu Ala Asn Trp 125	30 Ala Glu Ala Ile Leu 110 Val	Asp Val Ile Ser 95 Lys	Met Asp 80 Lev Arg
		Lys Leu Tyr 65 Val Asp Thr	Ala Val 50 Trp Leu Arg Pro Val	Pro 35 Ala Tyr Phe Tyr Arg 115 Ile	20 Gln Thr Phe Cys Trp 100 Arg	Asn Leu Gly Thr 85 Ser Ile	Leu Val Lys 70 Ser Ile Lys	Phe Ile 55 Val Ser Thr Ala Pro 135	Leu 40 Pro Trp Ile Gln Ile 120 Leu	25 Val Phe Cys Val Ala 105 Ile Leu	Ser Ser Glu His 90 Ile Val	Ile Leu Ile 75 Leu Glu Thr	Ala Ala 60 Tyr Cys Tyr Val Ile 140	Ser 45 Asn Leu Ala Asn Trp 125 Glu	30 Ala Glu Ala Ile Leu 110 Val Lys	Asp Val Ile Ser 95 Lys Ile Lys	Met Asp 80 Lev Arg

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					165					170					175	
	Cys	Leu	Ile	Asn 180	His	Leu	Val	Tyr	Val 185	Arg	Ile	Tyr	Gln	Ile 190	Ala	Lys
5	Arg	Arg	Thr 195	Arg	Val	Pro	Pro	Ser 200	Arg	Arg	Gly	Pro	Asp 205	Ala	Cys	Ser
	Ala	Pro 210	Pro	Gly	Gly	Ala	Asp 215	Arg	Arg	Pro	Asn	Ala 220	Val	Gly	Pro	Glu
	Arg 225	Gly	Ala	Gly	Thr	Ala 230	Gly	Gly	Gln	Gly	Glu 235	Glu	Arg	Ala	Gly	Gly 240
10	Ala	Lys	Ala	Ser	Arg 245	Trp	Arg	Gly	Arg	Gln 250	Asn	Arg	Glu	Lys	Arg 255	Phe
	Thr	Phe	Val	11e 260	Ala	Val	Val	Ile	Gly 265	Val	Phe	Val	Val	Cys 270	Trp	Phe
15	Pro	Phe	Phe 275	Phe	Thr	Tyr	Thr	Leu 280	Ile	Ala	Val	Gly	Cys 285	Pro	Val	Pro
	Tyr	Gln 290	Leu	Phe	Asn	Phe	Phe 295	Phe	Trp	Phe	Gly	Tyr 300	Cys	naA	Ser	Ser
	Leu 305	Asn	Pro	Val	Ile	Tyr 310	Thr	Ile	Phe	Asn	His 315	двр	Phe	Arg	Arg	Ala 320
20	Phe	Lys	Lys	Ile	Leu 325	Cys	Arg	Gly	Ąsp	Arg 330	Lys	Arg	Ile	Val		
	(2) INFO	SEQ	JENCE	CHA	ARAC	reri:	STICS	S:								
25	(ii)	(B) (C) (D)	TYI TYI TOI	PE: & RANDE	amino EDNE: GY:	s ac: SS: :	id sing: ar	acid:	5							
25	0.	(B) (C) (D) MOL	TYI STI	PE: & RANDI POLOC TYI	emino EDNE: GY: I	s ac: SS: : line: pept:	id sing: ar ide	le		: 23 :						
30	(xi) Leu 1	(B) (C) (D) MOLI SEQI	) TYI ) STI ) TOI ECULI UENCI	PE: a RANDI POLOG TYI E DES	amine SDNES SY: 1 PE: 1 SCRII	SS:   line pept: PTIO	id sing: ar ide N: SI	le EQ II Ser	D NO Val	Ile 10					15	
	(xi) Leu 1	(B) (C) (D) MOLI SEQI	) TYI ) STI ) TOI ECULI UENCI	PE: a RANDI POLOG TYI E DES	amine SDNES SY: 1 PE: 1 SCRII	SS:   line pept: PTIO	id sing: ar ide N: SI	le EQ II Ser	D NO Val	Ile 10					15	Ile <b>Ar</b> g
	(xi) Leu 1 Gly Ile	(B) (C) (D) (D) MOL SEQ Leu Leu Asn	) TYI ) STI ) TOI ECULI UENCE Thr Ile Gln 35	PE: 6 RANDI POLOCE TYI E DES Ala Leu 20 Asn	SCRII Leu 5 Val	o ac: SS:   line; pept: PTIO; Val Ile	id sing: ar ide N: Si Leu Leu	Ser Ser Val	Val Val 25 Ser	Ile 10 Phe Ile	Thr Ala	Tyr Val	Lys Ala 45	Pro 30 Asp	15 Leu Leu	Arg Thr
30	(xi) Leu 1 Gly Ile	(B) (C) (D) MOLI SEQUE Leu Asn Val Ala 50	) TYI ) STI ) TOI ECULI UENCI Thr Ile Gln 35	PE: & RANDE POLOCE TYI  Ala  Leu 20  Asn  Leu	SCRII  Leu  Val  Phe  Val	o ac: SS: !! linea pept: Val Val Ile Phe	id sing ar ide N: Sl Leu Leu Ile Pro	Ser Ser Val 40	Val Val 25 Ser	Ile 10 Phe Ile Ala	Thr Ala Tyr	Tyr Val Ser	Lys Ala 45 Ile	Pro 30 Asp	Leu Leu Gly	Arg Thr Arg
30	(xi) Leu 1 Gly Ile	(B) (C) (D) MOLI SEQUE Leu Asn Val Ala 50	) TYI ) STI ) TOI ECULI UENCE Thr Ile Gln 35	PE: & RANDE POLOCE TYI  Ala  Leu 20  Asn  Leu	SCRII  Leu  Val  Phe  Val	o ac: SS: !! linea pept: Val Val Ile Phe	id sing ar ide N: Sl Leu Leu Ile Pro	Ser Ser Val 40	Val Val 25 Ser	Ile 10 Phe Ile Ala	Thr Ala Tyr	Tyr Val Ser	Lys Ala 45 Ile	Pro 30 Asp	Leu Leu Gly	Arg Thr Arg
30	(xi) Leu 1 Gly Ile Val Trp 65	(B) (C) (D) (D) (D) (D) (D) (D) (D) (D) (D) (D	) TYI ) STI ) TOI ECULI UENCI Thr Ile Gln 35	PE: & RANDE POLOG TYI E DES Ala Leu 20 Asn Leu Gly	EDNES SY: 1 PE: 1 SCRII Val Phe Val Ile	PTION  Val  Ile  Phe  Leu  His  70	id sing ar ide N: SI Leu Leu Ile Pro 55 Leu	Ser Ser Val 40 Phe	Val Val 25 Ser Trp	Ile 10 Phe Ile Ala Leu	Thr Ala Tyr Trp 75	Tyr Val Ser 60 Leu	Lys Ala 45 Ile	Pro 30 Asp Leu Cys	Leu Leu Gly Asp	Arg Thr Arg Val
30	(xi) Leu 1 Gly Ile Val Trp 65 Leu	(B) (C) (D) MOLI SEQI Leu Asn Val Ala 50 Glu Cys	) TYI ) STI ) TOI ECULI UENCE  Thr  Ile  Gln 35  Leu  Phe  Cys	PE: & RANDE POLOG TYI E DES Ala Leu 20 Asn Leu Gly Thr	EMINGS SY: 1 PE: 1 SCRII Val Phe Val Ile Ser 85	PTION  Val  Ile  Phe  Leu  His  70	id sing: ar ide N: Si Leu Leu Ile Pro 55 Leu Ile	Ser Ser Val 40 Phe Cys	Val Val 25 Ser Trp Lys	Ile 10 Phe Ile Ala Leu Leu 90	Thr Ala Tyr Trp 75 Cys	Tyr Val Ser 60 Leu Ala	Lys Ala 45 Ile Thr	Pro 30 Asp Leu Cys	Leu Gly Asp Leu 95 Arg	Arg Thr Arg Val
30	(xi) Leu 1 Gly Ile Val Trp 65 Leu Arg	(B) (C) (D) MOLI SEQUE Leu Asn Val Ala 50 Glu Cys	) TYI ) STI ) TOI ECULI UENCE  Thr  Ile  Gln 35  Leu  Phe  Cys	PE: & RANDE POLOCE TYPE DES Ala Leu 20 Asn Leu Gly Thr Ala 100 Val	EMINGSONES SY: 1 PE: 1 SCRII Val Phe Val Ile Ser 85	PTION  Val  Ile  Phe  Leu  His  70  Ser	id sing: ar ide N: S! Leu Leu Ile Pro 55 Leu Ile Asp	Ser Ser Val 40 Phe Cys Leu	Val Val Ser Trp Lys Asn Ile 105 Ser	Ile 10 Phe Ile Ala Leu 90 Asn	Thr Ala Tyr Trp 75 Cys	Tyr Val Ser 60 Leu Ala	Lys Ala 45 Ile Thr	Pro 30 Asp Leu Cys Ala Lys 110	Leu Gly Asp Leu 95	Arg Thr Arg Val 80 Asp

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			130					135					140				
		Phe 145	Thr	Ser	Ala	Thr	Pro 150	Cys	Glu	Leu	Thr	Ser 155	Gln	Arg	Ile	Gly	Tyr 160
5		Val	Ile	Tyr	Ser	Ser 165	Leu	Gly	Ser	Phe	Phe 170	Ile	Pro	Ile	Ala	Ile 175	Met
		Arg	Ile	Val	Tyr 180	Ile	Glu	Ile	Phe	Val 185	Ala	Thr	Arg	Arg	Arg 190	Leu	Arg
		Glu	Arg	Ala 195	Arg	Ala	Asn	Lys	Ile 200	Asn	Thr	Ile	Ala	Leu 205	Lys	Ser	Thr
10		Glu	Leu 210	Glu	Pro	Met	Ala	Asn 215	Ser	Ser	Pro	Val	Ala 220	Ala	Ser	Asn	Ser
		Gly 225	Ser	Lys	Lys	Lys	Thr 230	Ser	Gly	Val	Asn	Gln 235	Phe	Ile	Glu	Glu	Lys 240
15		Gln	Lys	Ile	Ser	Leu 245	Ser	Lys	Glu	Arg	Arg 250	Ala	Ala	Arg	The	<b>Leu</b> 255	Gly
					260		Val			265					270		
		Val	Ile	<b>Leu</b> 275	Pro	Phe	Сув	Сув	Pro 280	Thr	Asn	Lys	Phe	<b>Lys</b> 285	Asn	Phe	Ile
20		Thr	Trp 290	Leu	Gly	Tyr	Ile	Asn 295	Ser	Gly	Leu	Asn	Pro 300	Val	Ile	Tyr	Thr
		Ile 305	Phe	Asn	Leu	Asp	Tyr 310	Arg	Arg	Ala	Phe	Lys 315	Arg	Leu	Leu	Gly	Leu 320
25		Asn															
	(2)	INFOR	TAMS	ON F	FOR S	SEQ 1	D NC	24:									
30		(i) (ii)	(A) (B) (C) (D)	LEN TYI STI TOI	NGTH: PE: & RANDE POLOG	373 mino DNES SY: 3	TERIS  ami aci SS: s lines	no a d singl	cids	<b>3</b>							
		(xi)				_	-		o ti	NIO -	24 •						
35		Arg 1	Ile	Leu	Thr	Ala 5	Cys	Phe	Leu	Ser	Leu 10	Leu	Ile	Leu	Ser	Thr 15	Leu
		Leu	Gly	Asn	Thr 20	Leu	Val	Cys	Ala	Ala 25	Val	Ile	Arg	Phe	Arg 30	His	Leu
		Arg	Ser	Lys 35	Val	Thr	Asn	Phe	Phe 40	Val	Ile	Ser	Leu	Ala 45	Val	Ser	Asp
40		Leu	Leu 50	Val	Ala	Val	Leu	Leu 55	Trp	Lys	Ala	Val	Ala 60	Glu	Ile	Ala	Gly
		Phe 65	Trp	Pro	Phe	Gly	Ser 70	Phe	Cys	Asn	Ile	Trp 75	Val	Ala	Phe	Asp	Ile 80
45		Met	Cys	Ser	Thr	Ala 85	Ser	Ile	Leu	Asn	Leu 90	Cys	Val	Ile	Ser	Val 95	Asp
		Arg	Tyr	Trp	Ala	Ile	Ser	Ser	Pro	Phe	Arg	Tyr	Glu	Arg	Lys	Lys	Arg

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					100					105					110		
		Pro	Lys	Ala 115	Ala	Phe	Ile	Leu	Ile 120	Ser	Val	Ala	Trp	Thr 125	Leu	Ser	Val
5		Leu	Ile 130	Ser	Phe	Ile	Pro	Val 135	Gln	Leu	Ser	Trp	His 140	Lys	Ala	Lys	Pro
		Thr 145	Ser	Pro	Ser	Asp	Gly 150	Met	Ala	Thr	Ser	Leu 155	Ala	Glu	Thr	Ile	Asp 160
		Asn	Сув	Asp	Ser	Ser 165	Leu	Ser	Arg	Thr	Tyr 170	Ala	Ile	Ser	Ser	Ser 175	Val
10		Ile	Ser	Phe	Tyr 180	Ile	Pro	Val	Ala	Ile 185	Leu	Val	Thr	Tyr	Thr 190	Arg	Ile
		_		Ile 195			-		200					205			
15			210	Val				215					220				
		225		Pro			230					235					240
2.0			-	Thr		245				_	250					255	
20				Phe	260					265					270		
				Pro 275		-		_	280					285			
25			290	Trp				295					300				
		305		Phe			310					315					320
3 N				Ala		325					330					335	
30				Met	340					345					350		
			-	Asn 355			Tyr	Leu	360	PIO	nis	AId	vai	365	ser	561	GIU
35	(2)	INFO	370	Lys			TIN NI	7.25									
40	(2)		SEQUAL (A)	UENC: ) LEI ) TY! ) STI	E CHI NGTH PE:	ARAC : 36	reri: 0 am: 0 ac:	STIC: ino a id	S: acid	s							
		(ii)	(D)	) TO	POLO	GY:	line	ar									
<b>4</b> 5		(xi) Gln 1	_	UENC: Thr					_			Ile	Ile	Trp	Thr	Leu 15	Leu
		Gly	Asn	Val	Leu 20	Val	Cys	Ala	Ala	Ile 25	Val	Arg	Ser	Arg	His 30	Leu	Leu

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	Val	Phe	Ile 35	Val	Ser	Ile	Ala	Val 40	Ser	Asp	Leu	Phe	Val 45	Ala	Leu	Leu
	Val	Asn 50	Thr	Trp	Lys	Ala	Tyr 55	Ala	Glu	Val	Ala	Gly 60	Tyr	Trp	Pro	Phe
5	Gly 65	Ala	Phe	Суѕ	Asp	Val 70	Trp	Val	Ala	Phe	Asp 75	Ile	Met	Cys	Ser	Thr 80
	Ala	Ser	Ile	Leu	Asn 85	Leu	Сув	Val	Ile	Ser 90	Val	qaA	Arg	Tyr	Trp 95	Ala
10	Ile	Ser	Arg	Pro 100	Phe	Arg	Tyr	Lys	Ala 105	Leu	Val	Met	Val	Gly 110	Ile	Ala
	Trp	Thr	Leu 115	Ser	Ile	Leu	Ile	Ser 120	Phe	Ile	Pro	Val	Gln 125	Ile	Asn	Trp
	Asn	Arg 130	qaA	Gln	Ala	Ala	Ser 135	Trp	Gly	Gly	Leu	Asp 140	Leu	Pro	Asn	Asn
15	Ile 145	Asp	Cys	qaA	Ser	Ser 150	Leu	Asn	Arg	Thr	Tyr 155	Ala	Ile	Ser	Ser	Ser 160
	Leu	Ile	Ser	Phe	Tyr 165	Ile	Pro	Val	Ala	Ile 170	Leu	Val	Thr	Tyr	Thr 175	Arg
20	Ile	Tyr	Arg	Ile 180	Ala	Gln	Val	Gln	Ile 185	Arg	Arg	Ile	Ser	Ser 190	Leu	Glu
	Arg	Ala	Ala 195	Glu	His	Ala	Gln	Ser 200	Cys	Arg	Ser	Ser	Ala 205	Ala	Cys	Ala
	Pro	Asp 210	Thr	Ser	Leu	Arg	Ala 215	Ser	Ile	Lys	Lys	Glu 220	Thr	Lys	Val	Leu
25	225					Ile 230					235					240
					245	Сув				250					255	
30	Gly	Pro	Pro	Ala 260	Gly	Phe	Pro	Cys	Val 265	Ser	Glu	Thr	Thr	Phe 270	Asp	Val
	Phe	Val	Trp 275	Phe	Gly	Trp	Ala	Asn 280	Ser	Ser	Leu	Asn	Pro 285	Val	Ile	Тут
	Ala	Phe 290	Asn	Ala	Asp	Phe	Gln 295	Lys	Val	Phe	Ala	Gln 300	Leu	Leu	Сув	Ser
35	His 305	Phe	Cys	Ser	Arg	Thr 310	Pro	Val	Glu	Thr	Val 315	Asn	Ile	Ser	Asn	Glu 320
	Leu	Ile	Ser	Tyr	Asn 325	Gln	Asp	Ile	Val	Phe 330	His	Lys	Glu	Ile	Ala 335	Ala
40	Ala	Tyr	Ile	His 340	Met	Met	Pro	Asn	Ala 345	Val	Thr	Pro	Gly	Asn 350	Arg	Glu
	Val	Asp	Asn 355	Asp	Glu	Glu	Glu	Gly 360								

(2) INFORMATION FOR SEQ ID NO:26:
 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 314 amino acids
 (B) TYPE: amino acid

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		(ii)	(D	) TO	POLO	GY:	SS: line pept:	ar	le								
5		(xi) Tyr 1					PTIO Thr					Leu	Ile	Ala	Va.	Ile 15	Val
		Phe	Gly	Asn	Val 20	Leu	Val	Сув	Met	Ala 25	Val	Ser	Arg	Glu	Lys 30	Ala	Leu
10		Gln	Thr	Met 35	Asn	Tyr	Leu	Ile	Val 40	Ser	Ile	Ala	Val	Ala 45	Asp	Leu	Leu
		Val	Ala 50	Thr	Leu	Val	Trp	Trp 55	Trp	Tyr	Leu	Glu	Val 60	Val	Gly	Glu	Trp
		Lys 65	Phe	Ser	Arg	Ile	His 70	Cys	Asp	Ile	Phe	<b>Va</b> l 75	Thr	Leu	Asp	Ile	Thr 80
15		Ala	Ser	Ile	Leu	Asn 85	Leu	Cys	Ala	Ile	Ser 90	Ile	qaA	Arg	Tyr	Thr 95	Ala
		Val	Ala	Met	Pro 100	Met	Leu	Tyr	Asn	Thr 105	Arg	Tyr	Ser	Ser	Lys 110	Arg	Arg
20		Val	Thr	Val 115	Met	Ile	Ser	Ile	Val 120	Trp	Val	Leu	Ser	Phe 125	Thr	Ile	Ser
		Сув	Pro 130	Leu	Leu	Phe	Gly	Leu 135	Asn	Asn	Ala	Asp	Gln 140	Asn	Glu	Cys	Ile
		Ile 145	Ala	Asn	Pro	Ala	Phe 150	Val	Val	Tyr	Ser	Ser 155	Ile	Val	Se₊	Phe	Tyr 160
25		Val	Pro	Phe	Ile	Val 165	Thr	Leu	Leu	Val	Tyr 170	Ile	Lys	Ile	Tyr	Ile 175	Val
		Leu	Arg	Arg	Arg 180	Arg	Lys	Arg	Val	Asn 185	Thr	Lys	Arg	Ser	Ser 190	Arg	Ala
30		Phe	Arg	Ala 195	His	Leu	Arg	Ala	Pro 200	Leu	Lys	Gly	Asn	Cys 205	Thr	His	Pro
		Glu	Asp 210	Met	Lys	Leu	Сув	Thr 215	Val	Ile	Pro	Asn	Gly 220	Lys	Thr	Arg	Thr
		225					Ser 230					235					240
35						245	Ile				250					255	
					260		Ile			265					270		
40		Asn	Ile	Pro 275	Pro	Val	Leu	Tyr	Ser 280	Ala	Phe	Thr	Trp	Leu 285	Gly	Tyr	Val
		Asn	Ser 290	Ala	Val	Asn	Pro	Ile 295	Ile	Tyr	Thr	Thr	Phe 300	Asn	Ile	Glu	Phe
. –		Arg 305	Lys	Ala	Phe	Leu	Lys 310	Ile	Leu	His	Cys						
7 L	(2)	THE	~~~~~														

- 45 (2) INFORMATION FOR SEQ ID NO:27: (i) SEQUENCE CHARACTERISTICS:

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5	(ii)	(B) (C) (D)	) LER ) TYI ) STI ) TOI ECULI	PE: a RANDE POLOG	mino DNES	s aci SS: s linea	id sing] ar		3							
	(xi) Ala 1		JENCI Tyr								Ile	Leu	Ala	Ile	Val 15	Phe
10	Gly	Asn	Gly	Leu 20	Val	Суѕ	Met	Ala	Val 25	Leu	Arg	Glu	Lys	Ala 30	Leu	Gln
	Thr	Thr	Thr 35	Asn	Tyr	Leu	Val	Val 40	Ser	Leu	Ala	Val	Ala 45	Asp	Leu	Leu
	Val	Ala 50	Thr	Leu	Val	Trp	Trp 55	Val	Val	Tyr	Leu	Glu 60	Val	Thr	Gly	Gly
15	Val 65	Trp	Asn	Phe	Ser	Arg 70	Ile	Cys	Cys	Asp	<b>Val</b> 75	Phe	Val	Thr	Leu	Asp 80
	Val	Met	Met	Thr	Ala 85	Ser	Ile	Leu	Asn	Leu 90	Cys	Ala	Ile	Ser	Ile 95	qaA
20	Arg	Tyr	Thr	Ala 100	Val	His	Tyr	Gln	His 105	Gly	Thr	Gly	Gln	Ser 110	Ser	Cys
	Arg	Arg	Val 115	Ala	Ile	Met	Ile	Thr 120	Ala	Val	Trp	Val	Leu 125	Ala	Phe	Ala
	Val	Ser 130	Сув	Pro	Leu	Leu	Phe 135	Gly	Phe	Asn	Thr	Gly 140	Asp	Pro	Thr	Val
25	Cys 145	Ser	Ile	Ser	Asn	Pro 150	Авр	Phe	Val	Ile	Tyr 155	Ser	Ser	Val	Val	Ser 160
	Phe	Tyr	Leu	Pro	Phe 165	Gly	Val	Thr	Val	Leu 170	Val	Tyr	Ala	Arg	Ile 175	Tyr
30	Val	Val	Leu	Lys 180	Gln	Arg	Arg	Arg	Lys 185	Arg	Ile	Leu	Thr	Arg 190	Gln	Asn
	Ser	Gln	Cys 195	Asn	Ser	Val	Arg	Pro 200	Gly	Phe	Pro	Gln	Gln 205	Ser	Thr	Ser
	Leu	Pro 210	Asp	Pro	Ala	His	Leu 215	Glu	Leu	Lys	Arg	Ser 220	Asn	Gly	Arg	Leu
35	Ser 225	Thr	Ser	Leu	Lys	Leu 230	Pro	Leu	Gln	Pro	Arg 235	Gly	Val	Pro	Leu	Arg 240
	Glu	Lys	Lys	Ala	Thr 245	Gln	Met	Val	Ala	Ile 250	Val	Leu	Gly	Ala	Phe 255	Ile
40	Val	Cys	Trp	Leu 260	Pro	Phe	Phe	Leu	Thr 265	His	Val	Ile	Asn	Thr 270	His	Cys
	Gln	Thr	Cys 275	His	Val	Ser	Pro	Glu 280	Leu	Tyr	Ser	Ala	Thr 285	Thr	Trp	Leu
	Gly	Tyr 290	Val	Asn	Ser	Ala	Leu 295	Asn	Pro	Val	Ile	Tyr 300	Thr	Thr	Phe	Asn
45	Ile 305	Glu	Phe	Arg	Lys	Ala 310	Phe	Leu	Lys	Ile	Leu 315	Ser	Сув			

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5	(2)		SEQU (A) (B) (C) (D)	JENCI LEI TYI STI	E CHANGTH PE: 8 RANDI POLO	ARAC: 315 mino EDNES SY: 3	reris 5 am: 5 ac: 5S: s linea	STICS ino a id sing: ar	S: acid:	5							
10		(xi) Gly 1	SEQU Ala									Leu	Ile	Cys	Ala	Val 15	Leu
		Ala	Gly	Asn	Ser 20	Leu	Val	Суѕ	Val	Ser 25	Val	Ala	Thr	Glu	Arg 30	Ala	Leu
		Gln	Thr	Pro 35	Thr	naA	Ser	Phe	Ile 40	Val	Ser	Leu	Ala	Ala 45	Ala	qaA	Leu
15		Leu	Leu 50	Ala	Leu	Leu	Val	Leu 55	Pro	Leu	Phe	Val	Tyr 60	Ser	Glu	Val	Gln
		Gly 65	Ala	Ala	Trp	Leu	Leu 70	Ser	Pro	Arg	Leu	Сув 75	Asp	Val	Met	Leu	Cys 80
20		Thr	Ala	Ser	Ile	Phe 85	Asn	Leu	Сув	Ala	Ile 90	Ser	Val	Asp	Àr	Phe 95	Val
		Ala	Val	Ala	Val 100	Pro	Leu	Arg	Tyr	Asn 105	Arg	Gln	Gly	Gly	Ser 110	Arg	Arg
		Gln	Leu	Leu 115	Leu	Ile	Gly	Ala	Thr 120	Trp	Leu	Leu	Ser	Ala 125	Ala	Val	Ala
25		Ala	Pro 130	Val	Leu	Суѕ	Gly	Leu 135	Asn	qaA	Val	Arg	Gly 140	Arg	Asp	Pro	Ala
		Val 145	Сув	Arg	Leu	Glu	<b>Asp</b> 150	Arg	Asp	Tyr	Val	Val 155	Tyr	Ser	Ser	Val	Cys 160
30		Ser	Phe	Phe	Leu	Pro 165	Cys	Pro	Leu	Leu	Tyr 170	Trp	Ala	Thr	Phe	Arg 175	Gly
		Leu	Gln	Leu	Val 180	Ala	Arg	Arg	Ala	Lys 185	Leu	His	Gly	Arg	Ala 190	Pro	Arg
		Arg	Pro	Ser 195	Gly	Pro	Gly	Pro	Pro 200	Ser	Pro	Thr	Pro	Pro 205	Ala	Pro	Arg
35		Leu	Pro 210	Gln	Asp	Pro	Сув	Gly 215	Ala	Leu	Pro	Pro	Gln 220	Thr	Pro	Pro	Gln
		Thr 225	Arg	Arg	Arg	Arg	Arg 230	Ala	Lys	Ile	Thr	Gly 235	Arg	Glu	Arg	Lys	Ala 240
40		Met	Arg	Val	Leu	Pro 245	Val	Val	Val	Gly	Ala 250	Phe	Ile	Leu	Cys	Trp 255	Thr
		Pro	Phe	Phe	Val 260	Val	His	Ile	Thr	Gln 265	Ala	Leu	Cys	Pro	Ala 270	Cys	Ser
		Val	Pro	Pro 275	Arg	Leu	Val	Ser	Ala 280	Val	Thr	Trp	Leu	Ser 285	Tyr	Val	Asn
45		Ser	Ala 290	Ile	Asn	Pro	Val	Ile 295	Tyr	Thr	Val	Phe	<b>As</b> n 300	Ala	Glu	Phe	Arg
		Asn	Val	Phe	Arg	Lys	Ala	Leu	Arg	Ala	Cys	Cys					

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5	(2)		SEQI (A (B (C (D	ION UENC LE TY TY TO TO	E CH NGTH PE: ( RAND) POLO	ARAC : 32 amin EDNE: GY:	TERI 7 am o ac SS: line	STIC ino id sing ar	S: acid	S							
10		(xi) Lys 1										Ile	Thr	Leu	Ala	Thr 15	Val
		Leu	Ser	Asn	Ala 20	Phe	Val	Leu	Thr	Arg 25	Ile	Leu	Leu	Thr	Arg 30	Lys	Leu
15		His	Thr	Pro 35	Ala	Asn	Tyr	Leu	Ile 40	Gly	Ser	Ile	Ala	Thr 45	Thr	Asp	Leu
		Leu	Val 50	Ser	Ile	Leu	Val	Trp 55	Ile	Ser	Ile	Ala	Tyr 60	Thr	Ile	Thr	His
		Thr 65	Trp	Asn	Phe	Gly	Gln 70	Ile	Leu	Cys	Asp	Ile 75	Trp	Leu	Ser	Ser	Asp 80
20		Ile	Thr	Сув	Суѕ	Thr 85	Ala	Ser	Ile	Leu	His 90	Leu	Сув	Val	Ile	Ala 95	Leu
		Asp	Arg	Tyr	Trp 100	Ala	Ile	Thr	Asp	Ala 105	Leu	Glu	Tyr	Ser	Lys 110	Arg	Arg
25		Thr	Ala	Gly 115	His	Ala	Ala	Thr	<b>M</b> et 120	Ile	Ala	Ile	Val	Trp 125	Ala	Ile	Ser
		Ile	Cys 130	Ile	Ser	Ile	Pro	Pro 135	Leu	Phe	Trp	Arg	Ala 140	Lys	Ala	Gln	Glu
		Glu 145	Met	Ser	qaA	Сув	Leu 150	Val	Asn	Thr	Ser	Gln 155	Ser	Tyr	Thr	Ile	Tyr 160
30				Сув		165					170					175	
				Arg	180					185					190		
35				Tyr 195					200					205			
			210	Ser				215					220				
		225		Val			230					235					240
40				Ala		245					250					255	
				Ala	260					265					27		
45		Val	Leu	Pro 275	Ile	Cys	Arg	Asp	Ser 280	Cys	Trp	Ile	His	Pro 285	Ala	Leu	Phe
		qaA	Phe 290	Phe	Thr	Trp	Leu	Gly 295	Tyr	Ile	Asn	Ser	Leu 300	Ile	Asn	Pro	Ile

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		Ile 305	Tyr	Thr	Val	Phe	Asn 310	Glu	Glu	Phe	Arg	Gln 315	Ala	Phe	Gln	Lys	Ile 320
		Val	Pro	Phe	Arg	Lys 325	Ala	Ser									
5	(2)		SEQU (A) (B) (C) (D)	JENCE LEM TYI STI TOI	CHANGTH: PE: 8 RANDI POLOC	ARACT 325 Anino EDNES 3Y:	TERIS  am: cac: SS: s  lines	STICS ino a id singl	S: acids	5							
		(xi)	SEQU		E DES	CRI	TIOI	N: SE				Ile	Phe	Cys	Ala	Val 15	Leu
15		Gly	Asn	Ala	Сув 20	Val	Val	Ala	Ala	Ile 25	Ala	Leu	Glu	Arg	Ser 30	Leu	Gln
		Asn	Val	Ala 35	Asn	Tyr	Leu	Ile	Gly 40	Ser	Leu	Ala	Val	Arg 45	Asp	Leu	Met
20		Val	Ser 50	Val	Leu	Val	Leu	Pro 55	Met	Ala	Ala	Leu	Tyr 60	Gln	Val	Leu	Asn
		Lys 65	Trp	Thr	Leu	Gly	Gln 70	Val	Thr	Сув	qaA	Leu 75	Phe	Ile	Ala	Leu	Asp 80
		Val	Leu	Сув	Сув	Thr 85	Ser	Ser	Ile	Leu	His 90	Leu	Cys	Ala	Ile	Ala 95	Leu
25		Ąsp	Arg	Tyr	Trp 100	Ala	Ile	Thr	Asp	Pro 105	Ile	qaA	Tyr	Val	As:1 110	Lys	Arg
		Thr	Pro	Arg 115	Pro	Arg	Ala	Leu	Ile 120	Ser	Leu	Thr	Trp	Leu 125	Ile	Gly	Phe
30		Leu	Ile 130	Ser	Ile	Pro	Pro	<b>Met</b> 135	Leu	Gly	Trp	Arg	Thr 140	Pro	Glu	qaA	Arg
		Ser 1 <b>4</b> 5	-	Pro	Asp	Ala	Cys 150	Thr	Ile	Ser	Lys	<b>As</b> p 155	His	Gly	Tyr	Thr	Ile 160
		Tyr	Ser	Thr	Ile	Phe 165	Ala	Phe	Tyr	Ile	Pro 170	Leu	Leu	Leu	Met	Leu 175	Val
35		Leu	Tyr	Gly	Arg 180	Ile	Phe	Arg	Ala	Ala 185	Arg	Phe	Arg	Ile	<b>A</b> rg 190	Lys	Thr
		Val	Lys	Lys 195	Val	Glu	Lys	Thr	Gly 200	Ala	Asp	Thr	Arg	His 205	Gly	Ala	Ser
40		Pro	Ala 210	Pro	Gln	Pro	Lys	Lys 215	Ser	Val	Asn	Gly	Glu 220	Ser	Gly	Ser	Arg
		Asn 225		Ser	Phe	Glu	Arg 230	Lys	Asn	Glu	Arg	Asn 235	Ala	Phe	Ala	Lys	Leu 240
		Leu	Ala	Arg	Glu	Arg 245	-	Thr	Val	Lys	Thr 250	Leu	Gly	Ile	IlJ	<b>M</b> et 2 <b>5</b> 5	
45		Phe	Ile	Leu	Cys 260	Trp	Leu	Pro	Phe	Phe 265	Ile	Val	Ala	Leu	Val 270	Leu	Pro
		Phe	Сув	Glu	Ser	Ser	Cys	His	Met	Pro	Thr	Leu	Ile	Arg	Ala	Ile	Ile

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				275					280					285			
		Asn	Trp 290	Leu	Сув	Val	Ile	Asn 295	Ser	Leu	Leu	Asn	Pro 300	Val	Ile	Tyr	Ala
5		Tyr 305	Phe	Asn	Lys	Asp	Phe 310	Gln	Asn	Ala	Phe	Lys 315	Lys	Ile	Ile	Lys	Cys 320
		Asn	Phe	Cys	Arg	Gln 325											
10	(2)	(ii)	SEQU (A) (B) (C) (D)	JENCE LEN TYI STI TOI	E CHA NGTH: PE: & RANDE POLOG	ARACT : 385 emino EDNES EY: 1	ERIS ami aci SS: s inea	STICS ino a id sing:	S: acids	5							
15		(xi) Gln l	SEQU Asn							_	_	Ile	Ile	Ile	Asn	Thr 15	Ile
		Gly	Gly	Asn	Ile 20	Leu	Val	Ile	Met	Ala 25	Val	Ser	Lys	Lys	Leu 30	His	Asn
20		Ala	Thr	Asn 35	Tyr	Phe	Leu	Met	Ser 40	Ile	Ala	Ile	Ala	Asp 45	Mer	Leu	Val
		Gly	Phe 50	Leu	Val	Trp	Leu	Ser 55	Leu	Leu	Ala	Ile	Leu 60	Tyr	qaA	Tyr	Val
25		Trp 65	Pro	Leu	Pro	Arg	Tyr 70	Leu	Cys	Pro	Val	Trp 75	Ile	Ser	Leu	Asp	Val 80
		Leu	Phe	Ser	Thr	Ala 85	Ser	Ile	Met	His	Leu 90	Сув	Ala	Ile	Ser	Leu 95	Asp
		Arg	Tyr	Val	Ala 100	Ile	Arg	Asn	Pro	11e 105	Glu	His	Ser	Arg	Phe 110	Ser	Arg
30		Thr	Lys	Ala 115	Ile	Met	Lys	Ile	Ala 120	Ile	Val	Trp	Ala	Ile 125	Ser	Ile	Gly
		Val	Ser 130	Val	Pro	Ile	Pro	Val 135	Ile	Gly	Leu	Arg	Asp 140	Glu	Ser	Lys	Val
35		Phe 145	Val	Asn	Asn	Thr	Thr 150	Ile	Сув	Val	Leu	<b>A</b> 5n 155	Asp	Pro	Asn	Phe	Val 160
		Leu	Ile	Gly	Ser	Phe 165	Val	Ala	Phe	Phe	Ile 170	Pro	Thr	Leu	Ile	<b>M</b> et 175	Val
		Ile	Thr	Tyr	Phe 180	Leu	Thr	Ile	Tyr	Val 185	Leu	Arg	Arg	Gln	Th. 190	Leu	Met
40		Leu	Leu	Arg 195	Gly	His	Thr	Glu	Glu 200	Glu	Ile	Ala	Met	Ser 205	Leu	Asn	Phe
		Leu	Asn 210	Cys	Cys	Cys	Lys	<b>Lys</b> 215	Asn	Gly	Gly	Glu	Glu 220	Glu	Asn	Ala	Pro
45		Asn 225	Asn	Pro	Asn	Pro	Asp 230	Gln	Lys	Pro	Arg	Arg 235	Lys	Lys	Lys	Glu	Lys 240
		Arg	Pro	Arg	Gly	Thr 245	Met	Gln	Ala	Ile	Asn 250	Asn	Glu	Lys	Lys	Ala 255	Ser

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	Lys	Val	Leu	Gly 260	Ile	Val	Phe	Phe	<b>Va</b> l 265	Phe	Leu	Ile	Met	Tro 270	Cys	Pro
	Phe	Phe	Ile 275	Thr	Asn	Ile	Leu	Ser 280	Val	Leu	Cys	Gly	Lys 285	Ala	Cys	Asn
5	Gln	Cys 290	Lys	Leu	Leu	Asn	Val 295	Phe	Val	Trp	Ile	Gly 300	Tyr	Val	Cys	Ser
	Gly 305		Asn	Pro	Val	Ile 310	Tyr	Thr	Leu	Phe	Asn 315	Lys	Ile	Tyr	Arg	Arg 320
10	Ala	Phe	Ser	Lys	Tyr 325	Leu	Arg	Cys	qaA	Tyr 330	Lys	Pro	Asp	Lys	Lys 335	Pro
	Pro	Val	Arg	Gln 340	Ile	Pro	Arg	Val	Ala 345	Ala	Thr	Ala	Leu	Ser 350	Gly	Arg
	Glu	Leu	<b>Asn</b> 355	Val	Asn	Ile	Tyr	Arg 360	His	Thr	Asn	Glu	Arg 365	Val	Ala	Arg
15	Lys	Ala 370	Asn	qaA	Pro	Glu	Pro 375	Gly	Ile	Glu	Asn	Gln 380	Val	Glu	Asn	Leu
	Glu 385															
20	(2) INFO (i)	SEQI (A)		GTH	ARACT	TERIS ami	TICS	3:	5							
			STI					le								
25	(ii)	MOLI	) TOI ECULI													
		SEQ! Asn									Val	Ile	Ile	Leu	Thr 15	Ile
30	Ala	Gly	Asn	Ile 20	Leu	Val	Ile	Met	Ala	Val	Ser	Leu	Glu		Lys	Leu
	Gln	Asn	Δla	_					25					30		
			35	Thr	Asn	Tyr	Phe	Leu 40	25	Ser		Ala	Ile 45		Asp	
	Leu	Leu 50	35			-		40	25 Met		Leu		45	Ala	Авр Туг	Met
35		50	35 Gly	Phe	Leu	Val	Trp 55	40 Val	25 Met Ser	Asn	Leu Glu	Thr 60	45 Ile	Ala Leu	•	<b>Met</b> Gly
35	Туг 65	50 Arg	35 Gly Trp	Phe Pro	Leu Leu	Val Pro 70	Trp 55 Ser	40 Val Lys	25 Met Ser Leu	Asn Cys	Leu Glu Ala 75	Thr 60 Ile	45 Ile Trp	Ala Leu Ile	туг	Met Gly Leu 80
35 40	Tyr 65 Asp	50 Arg Val	35 Gly Trp Leu	Phe Pro	Leu Leu Ser 85	Val Pro 70	Trp 55 Ser Ala	40 Val Lys Ser	25 Met Ser Leu Ile	Asn Cys Met 90	Leu Glu Ala 75 His	Thr 60 Ile Leu	45 Ile Trp Cys	Ala Leu Ile Ala	Tyr Tyr Ile	Met Gly Leu 80 Ser
	Tyr 65 Asp Leu	50 Arg Val Asp	35 Gly Trp Leu Arg	Phe Pro Phe Tyr	Leu Leu Ser 85 Val	Val Pro 70 Thr	Trp 55 Ser Ala Ile	40 Val Lys Ser Gln	Met Ser Leu Ile Asn 105	Asn Cys Met 90 Pro	Leu Glu Ala 75 His	Thr 60 Ile Leu	45 Ile Trp Cys	Ala Leu Ile Ala Ser	Tyr Tyr Ile	Met Gly Leu 80 Ser
	Tyr 65 Asp Leu Asn	50 Arg Val Asp	Gly Trp Leu Arg Arg 115 Gly	Phe Pro Phe Tyr 100	Leu Ser 85 Val	Val Pro 70 Thr Ala	Trp 55 Ser Ala Ile	Val Lys Ser Gln Leu 120	Met Ser Leu Ile Asn 105 Lys	Asn Cys Met 90 Pro	Leu Glu Ala 75 His Ile	Thr 60 Ile Leu His	11e Trp Cys His Val	Ala Leu Ile Ala Ser 110 Trp	Tyr Tyr Ile 95 Arg	Met Gly Leu 80 Ser Phe
	Tyr 65 Asp Leu Asn	Arg Val Asp Ser Val 130	Gly Trp Leu Arg Arg 115 Gly	Phe Pro Phe Tyr 100 Thr	Leu  Ser  85  Val  Lys  Ser	Val Pro 70 Thr Ala Ala	Trp 55 Ser Ala Ile Phe	Val Lys Ser Gln Leu 120	Met Ser Leu Ile Asn 105 Lys Pro	Asn Cys Met 90 Pro Ile Val	Leu Glu Ala 75 His Ile Ile	Thr 60 Ile Leu His Ala Gly 140	11e Trp Cys His Val 125 Leu	Ala Leu Ile Ala Ser 110 Trp Gln	Tyr Tyr Ile 95 Arg	Met Gly Leu 80 Ser Phe Ile

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		Val	Leu	Ile	Gly	Ser 165	Phe	Val	Ala	Phe	Phe 170	Ile	Pro	Leu	Thr	Ile 175	Met
		Val	Ile	Thr	Tyr 180	Phe	Leu	Thr	Ile	Lys 185	Ser	Leu	Arg	Gln	Lys 190	Phe	Ala
5		Thr	Leu	Cys 195	Val	Ser	Asp	Leu	Ser 200	Thr	Arg	Ala	Lys	Leu 205	Ala	Ser	Phe
		Ser	Phe 210	Leu	Pro	Gln	Ser	Ser 215	Leu	Ser	Ser	Glu	Lys 220	Leu	Phe	Gln	Arg
10		Ser 225	Ile	His	Arg	Glu	Pro 230	Gly	Ser	Tyr	Ala	Gly 235	Arg	Lys	Thr	Met	Gln 2 <b>4</b> 0
		Ser	Ile	Ser	Asn	Glu 245	Gln	Lys	Ala	Cys	Lys 250	Val	Leu	Gly	Ile	Val 255	Phe
		Phe	Leu	Phe	Val 260	Val	Met	Trp	Cys	Pro 265	Phe	Phe	Ile	Thr	Asn 270	Ile	Met
15		Val	Ile	Cys 275	Lys	Glu	Ser	Cys	Asn 280	Glu	Asn	Val	Ile	Gly 285	Ala	Leu	Leu
		Asn	Val 290	Phe	Val	Trp	Ile	Gly 295	Tyr	Leu	Ser	Ser	Ala 300	Val	Asn	Pro	Leu
20		Val 305	Tyr	Thr	Leu	Phe	Asn 310	Lys	Thr	Tyr	Arg	Ser 315	Ala	Phe	Ser	Arg	Tyr 320
		Leu	Gln	Сув	Gln	Tyr 325	Lys	Glu	Asn	Arg	Lys 330	Pro	Leu	Leu	Ile	Leu 335	Val
		Asn	Thr	Ile	Pro 340	Ala	Leu	Ala	Tyr	Lys 345	Ser	Ser	Gln	Leu	Gln 350	Val	Gly
25		Gln	Lys	Lys 355	naA	Ser	Gln	Glu	Asp 360	Ala	Glu	Gln	Thr	Val 365	Asp	Asp	Cys
		Ser	Met 370	Val	Thr	Leu	Gly	<b>Lys</b> 375	Gln	Gln	Ser	Glu					
30	(2)	(i)	SEQUAL (A)	JENCI LEI TYI STI	FOR S E CHANGTH: PE: 8 RANDI POLOX	ARACT : 33' amino EDNES	reris 7 am: 5 ac: 5S: 8	STICS ino a id sing:	S: acid:	5							
35		(ii)															
		(xi) Ile 1			Thr							Ile	Leu	Ile	Thr	Val 15	Ala
40		Gly	Asn	Val	Val 20	Val	Cys	Ile	Ala	Val 25	Gly	Ile	Asn	Arg	Arg 30	Leu	Arg
		Asn	Leu	Thr 35	Asn	Cys	Phe	Ile	Val 40	Ser	Leu	Ala	Ile	Thr 45	Asp	Leu	Leu
		Leu	Gly 50	Leu	Leu	Val	Leu	Pro 55	Phe	Ser	Ala	Ile	Tyr 60	Gln	Leu	Ser	Cys
45		Lys 65	Trp	Ser	Phe	Gly	Lys 70	Val	Phe	Cys	Asn	Ile 75	Tyr	Thr	S€1.	Leu	Asp 80
		Val	Met	Leu	Cys	Thr	Ala	Ser	Ile	Leu	Asn	Leu	Leu	Ile	Ser	Leu	qaA

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						85					90					95	
		Arg	Tyr	Сув	Ala 100	Val	Met	Asp	Pro	Leu 105	Arg	Tyr	Pro	Val	Leu 110	Val	Arg
5		Pro	Val	<b>A</b> rg 115	Val	Ala	Ile	Ser	Leu 120	Val	Leu	Ile	Trp	Val 125	Ile	Ser	Ile
		Thr	Leu 130	Ser	Phe	Leu	Ser	Ile 135	His	Leu	Gly	Trp	Asn 140	Ser	Arg	Asn	Glu
		Thr 145	Ser	Lys	Gly	Asn	His 150	Thr	Thr	Ser	Lys	Cys 155	Lys	Val	Gln	Val	Asn 160
1.0		Glu	Val	Tyr	Gly	Leu 165	Val	Asp	Gly	Leu	Val 170	Thr	Phe	Tyr	Leu	Pro 175	Leu
		Leu	Ile	Met	Сув 180	Ile	Thr	Tyr	Tyr	Arg 185	Ile	Phe	Lys	Val	Ala 190	Arg	Asp
15		Ala	Lys	Arg 195	Asn	His	Ile	Ser	Ser 200	Trp	Lys	Ala	Ala	Thr 205	Ile	Arg	Glu
			210					215					220	Phe			-
		Trp 225	Phe	Pro	Tyr	Phe	Thr 230	Ala	Phe	Val	Tyr	Arg 235	Gly	Leu	Arg	Gly	Asp 240
20		ĄaĄ	Ala	Ile	Asn	Glu 245	Val	Leu	Glu	Ala	11e 250	Val	Leu	Trp	Leu	Gly 255	Tyr
		Ala	Asn	Ser	Ala 260	Leu	asn	Pro	Ile	Leu 265	Tyr	Ala	Ala	Leu	Asn 270	Arg	Asp
25		Phe	Arg	Thr 275	Gly	Tyr	Gln	Gln	Leu 280	Phe	Cys	Сув	Arg	Ile 285	Ala	Asn	Arg
		Asn	Ser 290	His	Lys	Thr	Ser	Leu 295	Arg	Ser	Asn	Ala	Ser 300	Gln	Leu	Ser	Arg
		305					310					315	-	Pro		-	320
30		Gln	Val	Trp	Ser	Gly 325	Thr	Glu	Val	Thr	Ala 330	Pro	Gln	Gly	Ala	Thr 335	Asp
		Arg															
35	(2)	INFOR	SEQU (A) (B) (C)	JENCI LEI TYI	CHANGTH: PE: & RANDI	ARACT 315 mino SDNES	TERIS ami ac:	STICS ino a id singl	S: acida	5							
10		(ii) (xi)				-	•		-O T	n NO	. 24 .						
												Phe	Val	Leu	Gly	Val 15	Leu
<b>1</b> 5		Gly	Asn	Gly	Leu 20	Val	Ile	Trp	Val	Ala 25	Gly	Phe	Arg	Met	Thr 30	His	Thr
		Val	Thr	Thr	Ile	Ser	Tyr	Leu	Asn	Leu	Ala	Val	Ala	Asp	Phe	Cys	Phe

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				35					40					45			
		Thr	Ser 50	Thr	Leu	Pro	Phe	Phe 55	Met	Val	Arg	Leu	Gly 60	His	Trp	Pro	Phe
5		Gly 65	Trp	Phe	Leu	Cys	Lys 70	Phe	Leu	Phe	Thr	Ile 75	Val	Asp	Ile	Asn	Leu 80
		Phe	Gly	Ser	Val	Phe 85	Leu	Ile	Ala	Leu	Ile 90	Ala	Leu	Asp	Arg	Cys 95	Val
		Cys	Val	Leu	His 100	Pro	Val	Trp	Thr	Gln 105	Asn	His	Arg	Thr	Val 110	Ser	Leu
10		Ala	Lys	Lys 115	Val	Ile	Ile	Gly	Pro 120	Trp	Val	Met	Ala	Leu 125	Leu	Leu	Thr
		Leu	Pro 130	Val	Ile	Ile	Arg	<b>Val</b> 135	Thr	Ile	Val	Pro	Gly 1 <b>4</b> 0	Lys	Thr	Gly	Thr
15		Val 145	Ala	Cys	Thr	Phe	Asn 150	Phe	Ser	Pro	Trp	Thr 155	Asn	Asp	Pro	Lys	Glu 160
		Arg	Ile	Asn	Val	Ala 165	Val	Ala	Met	Leu	Thr 170	Val	Arg	Gly	Ile	Ile 175	Arg
		Phe	Ile	Ile	Gly 180	Phe	Ser	Ala	Pro	<b>M</b> et 185	Ser	Ile	Val	Ala	Val 199	Ser	Tyr
20		Gly	Leu	Ile 195	Ala	Thr	Lys	Ile	Ile 200	Lys	Ser	Ser	Arg	Pro 205	Leu	Arg	Val
		Leu	Ser 210	Phe	Val	Ala	Ala	Ala 215	Phe	Phe	Leu	Сув	Trp 220	Ser	Pro	Tyr	Gln
25		Val 225	Val	Ala	Leu	Ile	Ala 230	Thr	Val	Arg	Ile	Arg 235	Glu	Leu	Leu	Gln	Gly 240
		Met	Tyr	Lys	Glu	Ile 245	Gly	Ile	Ala	Val	Asp 250	Val	Thr	Ser	Ala	Ile 255	Ala
		Phe	Phe	Asn	Ser 260	Cys	Leu	Asn	Pro	Leu 265	Tyr	Val	Phe	Met	Gly 270	Gln	qaA
30		Phe	Arg	Glu 275	Arg	Leu	Ile	His	Ala 280	Leu	Pro	Ala	Ser	Leu 285	Glu	Arg	Ala
		Leu	Thr 290	Glu	Asp	Ser	Thr	Gln 295	Thr	Ser	Asp	Thr	Ala 300	Thr	Asn	Ser	Thr
35		Leu 305	Pro	Ser	Ala	Glu	<b>Val</b> 310	Ala	Leu	Gln	Ala	Lys 315					
10	(2)	INFOR	SEQU (A) (B) (C) (D)	JENCE LEN TYE STE TOE	E CHANGTH: PE: 6 RANDE	ARACT 304 mino EDNES SY: ]	TERIS  ami caci SS: s  linea	STICS ino a id singl	S: acids	;							
		(xi)	SEQU		E DES	CRIE	TION	Y: SE				Val	Phe	יום.]	Val	Glv	Val
15		1				5					10					15	
		⊥eu	GTÅ	Asn	ATA	ren	vai	val	ıπρ	val	Inr	Ala	ьиe	GII	ATA	гàг	Arg

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					20					25					30		
		Thr	Ile	Asn 35	Ala	Ile	Trp	Phe	Leu 40	Asn	Ile	Ala	Val	Ala 45	Asp	Phe	Leu
5		Ser	Cys 50	Leu	Ala	Leu	Pro	Ile 55	Leu	Phe	Thr	Ser	Ile 60	Val	Gln	His	His
		His 65	Trp	Pro	Phe	Gly	Gly 70	Ala	Ala	Cys	Ser	Ile 75	Leu	Pro	Ser	Leu	Ile 80
		Leu	Leu	Asn	Met	Tyr 85	Ala	Ser	Ile	Leu	Leu 90	Leu	Ala	Thr	Ile	Ser 95	Ala
10		Дæр	Arg	Phe	Leu 100	Leu	Val	Phe	Lys	Pro 105	Ile	Trp	Сув	Gln	Asn 110	Phe	Arg
		Gly	Ala	Gly 115	Leu	Ala	Trp	Ile	Ala 120	Cys	Ala	Val	Ala	Trp 125	Gly	Ile	Ala
15		Leu	Leu 130	Leu	Thr	Ile	Pro	Ser 135	Phe	Leu	Tyr	Arg	Val 140	Val	Arg	Glu	Glu
		Tyr 145	Phe	Pro	Pro	Lys	Val 150	Leu	Cys	Gly	Cys	Asp 155	Tyr	Ser	His	Asp	Lys 160
		Arg	Arg	Glu	Arg	Ala 165	Val	Ala	Ile	Val	Arg 170	Leu	Val	Leu	Gly	Phe 175	Leu
20		Trp	Pro	Leu	Leu 180	Thr	Leu	Thr	Ile	Cys 185	Tyr	Thr	Thr	Arg	Ser 190	Thr	Lys
		Thr	Leu	Lys 195	Val	Val	Val	Ala	Val 200	Val	Ala	Ser	Phe	Phe 205	Ile	Phe	Trp
25		Leu	Pro 210	Tyr	Gln	Val	Thr	Gly 215	Ile	Met	Met	Ser	Phe 220	Leu	Glu	Pro	Ser
		Ser 225	Pro	Thr	Phe	Leu	Leu 230	Leu	Asn	Lys	Leu	Asp 235	Ser	Leu	Cys	Val	Ser 240
		Phe	Ala	Tyr	Ile	Asn 245	Cys	Cys	Ile	Asn	Pro 250	Ile	Ile	Tyr	Val	Val 255	Ala
30		Gly	Gln	Gly	Gln 260	Phe	Gln	Gly	Arg	Leu 265	Arg	Lys	Ser	Leu	Pro 270	Ser	Leu
		Leu	Arg	Asn 275	Val	Leu	Thr	Glu	Glu 280	Ser	Val	Val	Arg	Glu 285	Ser	Lys	Ser
35		Phe	Thr 290	Arg	Ser	Thr	Val	<b>As</b> p 295	Thr	Met	Ala	Gln	Lys 300	Thr	Gln	Ala	Val
40	(2)		SEQI (A (B (C	ION DENCE TYPE TYPE TYPE TYPE TYPE TYPE TYPE	E CHA NGTH PE: 8 RANDI	ARAC : 32: amin EDNE:	reri: 2 am: 5 ac: SS:	STIC: ino a id sing:	S: acid:	s							
		(ii) (xi)	MOL		E TY	PE: ]	pept	ide	RO TI	חוא ם	.36.						
45				Phe								Val	Phe	Val	Val	Ser 15	Leu
		Pro	Leu	Asn	Ile	Met	Ala	Ile	Val	Val	Phe	Ile	Leu	Lys	Mer	Lys	Val

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				20					25					30		
	Lys	Lys	Pro 35	Ala	Val	His	Ile	Ala 40	Thr	Ala	Asp	Val	Leu 45	Phe	Val	Ser
5	Val	Leu 50	Pro	Phe	Lys	Ile	Ser 55	Tyr	Tyr	Phe	Ser	Gly 60	Ser	Asp	Trp	Glr
	Phe 65	Gly	Ser	Glu	Leu	Cys 70	Arg	Phe	Val	Thr	Ala 75	Ala	Phe	Tyr	Cys	Asr 80
	Met	Tyr	Ala	Ser	Ile 85	Leu	Leu	Ile	Ser	Ile 90	Asp	Arg	Phe	Ile	Ala 95	Va]
10	Val	Tyr	Pro	<b>Met</b> 100	Gln	Ser	Leu	Ser	Trp 105	Arg	Thr	Leu	Gly	<b>A</b> rg 110	Ala	Ser
	Phe	Thr	Сув 115	Ile	Ala	Ile	Trp	Ala 120	Ile	Ala	Ile	Ala	Gly 125	Val	Pro	Let
15	Val	Leu 130	Lys	Glu	Gln	Thr	Ile 135	Gln	Val	Pro	Gly	Leu 140	Asn	Ile	Thr	Thr
	Ile 145	Cys	His	qaA	Val	Leu 150	Asn	Glu	Thr	Leu	Leu 155	Glu	Gly	Tyr	Tyr	Ala 160
	Tyr	Tyr	Phe	Ser	Ala 165	Phe	Ser	Ala	Val	Phe 170	Phe	Phe	Val	Pro	Leu 175	Ile
20	Ile	Ser	Thr	Val 180	Суѕ	Tyr	Val	Ser	Ile 185	Ile	Arg	Cys	Leu	Ser 190	Ser	Ser
	Ala	Val	Ala 195	Asn	Arg	Ser	Lys	Lys 200	Ser	Arg	Thr	Asn	Arg 205	Сув	Phe	Asr
25	Ser	Thr 210	Val	Ala	Leu	Phe	Leu 215	Ser	Ala	Ala	Val	Phe 220	Суз	Ile	Phe	Ile
	Ile 225	сув	Phe	Gly	Pro	Thr 230	Trp	Leu	Leu	Ile	Ala 235	His	Tyr	Ser	Phe	Leu 240
	Ser	His	Thr	Ser	Thr 245	Thr	Glu	Ala	Ala	Tyr 250	Phe	Ala	Tyr	Leu	<b>Le</b> u 255	Сув
30	Val	Cys	Val	Ser 260	Ser	Ile	Ser	Ser	Cys 265	Ile	qaA	Pro	Leu	Ile 270	Tyr	Tyr
	Tyr	Ala	Ser 275	Ser	Glu	Сув	Gln	Arg 280	Tyr	Val	Tyr	Ser	Ile 285	Leu	Сув	Cys
35	Lys	Glu 290	Ser	Ser	Asp	Pro	Ser 295	Ser	Tyr	Asn	Ser	Ser 300	Gly	Gln	Leu	Met
	Ser 305	Leu	Thr	Сув	Ser	Ser 310	Asn	Leu	Asn	Asn	Ser 315	Ile	Tyr	Lys	Lys	Leu 320
	Leu	Thr														

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	7	ki) Tyr l	SEQU Ile	JENCE Asn	DES Thr	CRIF Val 5	TION Ile	I: SE Ser	Cys	NO:	37: Ile 10	Phe	Ile	Val	Gly	Trp 15	Gly
5	I	Asn	Ala	Thr	Leu 20	Leu	Arg	Ile	Ile	Tyr 25	Gln	Asn	Lys	Cys	Met 30	Arg	Asn
	C	Gly	Pro	Asn 35	Ala	Leu	Ile	Ala	Ser 40	Ile	Ala	Leu	Gly	Asp 45	Leu	Ile	Tyr
	Ţ	Jal	Val 50	Ile	qaA	Leu	Pro	lle 55	Asn	Val	Pro	Lys	Leu 60	Ile	Ala	Gly	Arg
10		rp 55	Pro	Phe	Glu	Gln	Asn 70	qaA	Phe	Gly	Val	Phe 75	Сув	Lys	Phe	Met	Gly 80
	7	Jal	Val	Met	Ile	Phe 85	Phe	Gly	Leu	Ser	Pro 90	Leu	Leu	Leu	Gly	Ala 95	Ala
15	ŀ	Met	Ala	Ser	Glu 100	Arg	Tyr	Leu	Gly	Ile 105	Thr	Arg	Pro	Phe	Ser 110	Arg	Pro
	1	Ala	Val	Ala 115	Ser	Gln	Arg	Arg	Ala 120	Trp	Ala	Thr	Val	Gly 125	Leu	Val	Trp
	7	Ala	Ala 130	Ala	Leu	Ala	Leu	Gly 135	Leu	Leu	Pro	Leu	Leu 140	Gly	Val	Gly	Arg
20		Tyr 145	Thr	Val	Gln	Tyr	Pro 150	Gly	Ser	Trp	Cys	Phe 155	Leu	Thr	Leu	Gly	Ala 160
	C	Glu	Ser	Gly	qaA	Val 165	Ala	Phe	Gly	Leu	Leu 170	Phe	Ser	Gly	Lev	Ser 175	Val
25	C	Gly	Leu	Ser	Phe 180	Leu	Leu	Asn	Thr	Val 185	Ser	Val	Ala	Thr	Leu 190	His	His
	7	Val	Tyr	His 195	Gly	Gln	Glu	Ala	Ala 200	Gln	Gln	Arg	Pro	Arg 205	Asp	Ser	Glu
	7	Val	Glu 210	Met	Met	Ala	Gln	Leu 215	Leu	Gly	Ile	Met	Val 220	Val	Ala	Ser	Val
30		Сув 225	Trp	Leu	Pro	Leu	Leu 230	Val	Phe	Ile	Ala	Gln 235	Thr	Val	Leu	Arg	Asn 240
	1	Pro	Pro	Ala	Met	Ser 245	Pro	Ala	Gly	Gln	Leu 250	Ser	Arg	Thr	Thr	Glu 255	Lys
35	(	Glu	Leu	Leu	Ile 260	Tyr	Leu	Arg	Val	<b>Ala</b> 265	Thr	Trp	Asn	Gln	Ile 270	Leu	Asp
	1	Pro	Trp	Val 275	Tyr	Ile	Leu	Phe	Arg 280	Arg	Ala	Val	Leu	Arg 285	Arg	Leu	Gln
	1	Pro	Arg 290	Leu	Ser	Thr	Arg	Pro 295	Arg	Ser	Leu	Ser	Leu 300	Gln	Pro	Gln	Leu
40		Thr 305	Gln	Arg	Ser	Gly	Leu 310	Gln									
<b>4</b> 5	(2) I		SEQI (A (B (C	JENCI ) LEI ) TY! ) STI	E CHA NGTH PE: A RAND	SEQ ARAC : 31: emine EDNE: GY:	reris 2 am: 5 ac: 88:	STIC: ino a id sing:	S: acid:	5							

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		(ii)	MOLI	CULE	TYP	E: p	pepti	de									
		(xi) Lys 1	SEQU Tyr	JENCI Phe	E DES Val	CRIF Val 5	PTION Ile	I: SE Ile	Q II Tyr	NO: Ala	:38: Leu 10	Val	Phe	Leu	Leu	Ser 15	Leu
5		Leu	Gly	Asn	Ser 20	Leu	Val	Met	Leu	Val 25	Ile	Leu	Tyr	Ser	Arg 30	Gly	Val
		Arg	Ser	Val 35	Thr	Ile	Val	Tyr	Leu 40	Leu	Asn	Ile	Ala	Ile 45	Ala	qaA	Leu
10		Leu	Phe 50	Ala	Leu	Thr	Leu	Pro 55	Ile	Trp	Ala	Ala	Ser 60	Lys	Val	Asn	Gly
		Trp 65	Ile	Phe	Gly	Thr	Phe 70	Leu	Сув	Lys	Trp	Ser 75	Leu	Leu	Lys	Glu	Val 80
		Asn	Phe	Tyr	Ser	Gly 85	Ile	Leu	Leu	Leu	Ala 90	Сув	Ile	Ser	Val	Asp 95	Arg
15		Tyr	Leu	Ala	Ile 100	Val	Arg	Ala	Thr	Arg 105	Thr	Leu	Thr	Gln	Lys 110	Arg	His
		Leu	Val	<b>L</b> ув 115	Phe	Ile	Сув	Leu	Ser 120	Ile	Trp	Gly	Leu	Ser 125	Leu	Leu	Leu
20		Ala	Leu 130	Pro	Val	Leu	Leu	Phe 135	Arg	Arg	Thr	Val	Tyr 140	Ser	Ser	Asn	Val
		Ser 145	Pro	Ala	Сув	Tyr	Glu 150	qaA	Met	Gly	Asn	Asn 155	Tyr	Ala	Asn	Trp	Arg 160
		Met	Leu	Leu	Pro	Ile 165	Leu	Pro	Gln	Ser	Phe 170	Gly	Phe	Ile	Val	Pro 175	Leu
25		Leu	Ile	Met	Leu 180	Tyr	Сув	Tyr	Gly	Phe 185	Thr	Leu	Arg	Thr	Leu 190	Phe	Lys
		Ala	Ile	Met 195	Gly	Gln	Lys	His	<b>A</b> rg 200	Ala	Met	Arg	Val	Ile 205	Phe	Ala	Val
30		Val	Leu 210	Ile	Phe	Leu	Leu	Cys 215	Trp	Leu	Pro	Tyr	Asn 220	Leu	Val	Leu	Ile
		Ala 225	Asp	Thr	Leu	Met	Arg 230	Thr	Gln	Val	Ile	Gln 235	Glu	Thr	Cys	Glu	Arg 240
		Arg	Asn	His	Ile	Asp 245	Arg	Ala	Ile	Asp	Ala 250	Thr	Glu	Ile	Leu	Gly 255	Ile
35		Leu	His	Ser	Cys 260	Leu	Asn	Pro	Leu	Ile 265	Tyr	Ala	Phe	Ile	Gly 270	Gln	Lys
		Phe	Arg	His 275	Gly	Leu	Leu	Lys	Ile 280	Leu	Ala	Ile	His	Gly 285	Leu	Ile	Ser
<b>4</b> 0		Lys	<b>Asp</b> 290	Ser	Leu	Pro	Lys	<b>As</b> p 295	Ser	Arg	Pro	Ser	Phe 300	Val	Gly	Ser	Ser
		Ser 305	Gly	His	Thr	Ser	Thr 310	Thr	Leu								
	(2)	INFO	RMAT:	ION	FOR !	SEO :	ID N	0:39	:								

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 326 amino acids
(B) TYPE: amino acid

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	(ii)	(D)	TOP	OLOC	Y: 1	inea		e								
	(xi)	SEQU	JENCE	DES	CRIE	OIT	: SE	Q II	NO:	39:						
5	Leu 1	Phe	Pro	Ile	Val 5	Tyr	Ser	Ile	Ile	Phe 10	Val	Leu	Gly	Ile	Ile 15	Ala
	Asn	Gly	Tyr	Val 20	Leu	Trp	Val	Phe	Ala 25	Arg	Leu	Tyr	Pro	Ser 30	Lys	Lys
10	Asn	Glu	Ile 35	Lys	Ile	Phe	Met	Val 40	Asn	Leu	Thr	Val	Ala 45	Asp	Leu	Leu
	Phe	Leu 50	Ile	Thr	Leu	Pro	Leu 55	Trp	Ile	Val	Tyr	Tyr 60	Ser	Asn	Gln	Gly
	Asn 65	Trp	Phe	Leu	Pro	Lys 70	Phe	Leu	Cys	Asn	Leu 75	Ala	Gly	Cys	Leu	Phe 80
15	Phe	Ile	Asn	Thr	Tyr 85	Сув	Ser	Val	Ala	Phe 90	Leu	Gly	Val	Ile	Thr 95	Tyr
	Asn	Arg	Phe	Gln 100	Ala	Val	Lys	Tyr	Pro 105	Ile	Lys	Thr	Ala	Gln 110	Ala	Thr
20	Thr	Arg	<b>Lys</b> 115	Arg	Gly	Ile	Ala	Leu 120	Ser	Leu	Val	Ile	Trp 125	Val	Ala	Ile
	Val	Ala 130	Ala	Ala	Ser	Tyr	Phe 135	Leu	Val	Met	Met	Asp 140	Ser	Thr	Asn	Val
	Val 145	Ser	Asn	Lys	Ala	Gly 150	Ser	Gly	Asn	Ile	Thr 155	Arg	ayɔ	Phe	Glu	<b>Arg</b> 160
25	Tyr	Glu	Lys	Gly	Ser 165	Lys	Pro	Val	Leu	Ile 170	Ile	His	Ile	Cys	Ile 175	Val
	Leu	Gly	Phe	Phe 180	Ile	Val	Phe	Leu	Leu 185	Ile	Leu	Phe	Cys	<b>As</b> n 190	Leu	Val
30	Ile	Ile	His 195	Thr	Leu	Leu	Arg	Gly 200	Pro	Val	Lys	Gln	Gln 205	Arg	Asn	Ala
	Glu	Val 210	Arg	Arg	Arg	Ala	Leu 215	Trp	Met	Val	Суѕ	Thr 220	Val	Ile	Ala	Val
	Phe 225	Val	Ile	Сув	Phe	Val 230	Pro	His	His	Met	Val 235	Gln	Leu	Pro	Trp	Thr 240
35	Leu	Ala	Glu	Leu	Cly 245	Met	Trp	Pro	Ser	Ser 250	Asn	His	Gln	Ala	Ile 255	Asn
	Asp	Ala	His	Gln 260	Val	Thr	Leu	Cys	Leu 265	Leu	Ser	Thr	Asn	Cys 270	Val	Leu
40	Asp	Pro	Val 275	Ile	Tyr	Сув	Phe	Leu 280		Lys	Lys	Phe	Arg 285	Lys	His	Leu
	Ser	Glu 290	Lys	Leu	Asn	Ile	<b>M</b> et 295		Ser	Ser	Gln	Lys 300		Ser	Arg	Val
	Thr 305	-	Asp	Thr	Gly	Thr 310	Glu	Met	Ala	Ile	Pro 315		Asn	His	Thr	Pro 320
45	Val	Asn	Pro	Ile	Lys	Asn										

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5	(2)		SEQUAL (A) (B) (C) (D)	JENCE LEN TYI STI TOI	CHA NGTH: PE: & RANDE POLOC	ARACT 333 mino EDNES SY: 1	TERIS  ami  aci  S:  inea	STICS ino a id sing] ar	S: acids	5							
10		(xi) Tyr 1		JENCE Asn								Phe	Val	Leu	Gly	Ile 15	Ile
		Gly	naA	Ser	Thr 20	Leu	Leu	Arg	Ile	Ile 25	Tyr	Lys	Asn	Lys	Суз 30	Met	Arg
15		Asn	Gly	Pro 35	Asn	Ile	Leu	Ile	Ala 40	Ser	Ile	Ala	Leu	Gly 45	qaA	Leu	Leu
		His	Ile 50	Ile	Ile	Asp	Ile	Pro 55	Ile	Met	Ala	Tyr	Lys 60	Leu	Ile	Ala	Gly
		<b>А</b> вр 65	Trp	Pro	Phe	Ala	Cys 70	Lys	Leu	Phe	Pro	Phe 75	Leu	Gln	Lys	Ser	Ser 80
20		Val	Gly	Ile	Thr	Val 85	Leu	Asn	Leu	Сув	Ala 90	Leu	Ser	Val	Asp	Arg 95	Tyr
		Arg	Ala	Val	Ala 100	Ser	Trp	Ser	Arg	Val 105	Gln	Gly	Ile	Gly	Ile 110	Pro	Leu
25		Val	Thr	Ala 115	Ile	Glu	Ile	Val	Ser 120	Ile	Trp	Ile	Leu	Ser 125	Phe	Ile	Leu
		Ala	Ile 130	Pro	Glu	Ala	Ile	Gly 135	Phe	Trp	Met	Val	Pro 140	Phe	Glu	Tyr	Lys
		Gly 1 <b>4</b> 5	Ala	Gln	His	Arg	Thr 150	Cys	Met	Leu	Asn	Ala 155	Thr	Ser	Lys	Leu	Phe 160
30		Tyr	Gln	Asp	Val	Lys 165	Asp	Trp	Trp	Leu	Phe 170	Gly	Phe	Tyr	Phe	Leu 175	Leu
		Val	Сув	Thr	Ala 180	Ile	Phe	Tyr	Thr	Leu 185	Met	Thr	Cys	Glu	<b>Met</b> 190	Leu	Asn
35		Arg	Arg	<b>Asn</b> 195	Gly	Ser	Leu	Arg	Ile 200	Ala	Leu	Ser	Glu	His 205	Leu	Lys	Gln
		Arg	<b>Arg</b> 210	Glu	Val	Ala	Lys	Thr 215	Val	Phe	Сув	Leu	Val 220	Val	Ile	Phe	Ala
		Leu 225	Сув	Trp	Phe	Pro	Leu 230	His	Leu	Ser	Arg	Ile 235	Leu	Lys	Lys	Thr	Val 240
40		Tyr	Asp	Glu	Met	Asp 245	Thr	Asn	Arg	Сув	Glu 250	Leu	Leu	Ser	Phe	Leu 255	Leu
		Leu	Met	Tyr	11e 260	Gly	Ile	Asn	Thr	Ala 265	Thr	Met	Ser	Cys	Ile 27ĵ	Asn	Pro
45		Ile	Ala	Leu 275	Tyr	Phe	Val	Ser	Lys 280	Lys	Phe	Lys	Asn	Cys 285	Phe	Gln	Ser
		Cys	Leu 290	Cys	Cys	Cys	Cys	Tyr 295	Gln	Ser	Lys	Ser	Ile 300	Met	Thr	Ser	Val

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		Pro 305	Met	Gln	Gly	Thr	Ser 310	Ile	Gln	Trp	Lys	Asn 315	His	Glu	Gln	Asn	Asn 320
		His	Asn	Thr	Glu	Arg 325	Ser	Ser	His	Lys	Asp 330	Ser	Ile	Asn			
5	(2)		SEQU (A) (B) (C) (D)	ENCE LEN TYP STR TOP	CHA IGTH: PE: 6 VANDE POLOC	RACT 350 mino SDNES Y: ]	TERIS  ami  aci  SS: s  lines	STICS ino a id singl	S: acids	5							
		(xi) Leu 1						N: SE Phe				Phe	Сув	Val	Va <u>l</u>	Gly 15	Leu
15		Ala	Ser	Asn	Leu 20	ьеu	Ala	Leu	Ser	Val 25	Leu	Ala	Gly	Ala	Arg 30	Gln	Ser
		Ser	Ser	<b>His</b> 35	Thr	Arg	Ser	Ser	Phe 40	Leu	Thr	Phe	Leu	Cys 45	Gly	Leu	Val
20		Leu	Thr 50	Leu	qaA	Phe	Leu	Gly 55	Leu	Leu	Val	Thr	Gly 60	Thr	Ile	Val	Val
		Ser 65	Gln	His	Ala	Ala	Leu 70	Phe	Glu	Trp	His	Ala 75	Val	qaA	Pro	Gly	Cys 80
		Arg	Leu	Сув	Arg	Leu 85	Val	Pro	Phe	Ile	Gln 90	Lys	Ala	Ser	Val	Gly 95	Ile
25		Thr	Val	Leu	Ser 100	Leu	Сув	Ala	Leu	Ser 105	Ile	qaA	Arg	Tyr	Arg 110	Ala	Val
		Ala	Ser	Trp 115	Ser	Arg	Ile	Lys	Gly 120	Ile	Gly	Val	Pro	Lys 125	Trp	Thr	Ala
30		Val	Glu 130	Ile	Val	Leu	Ile	Trp 135	Val	Val	Ser	Val	Val 140	Leu	Ala	Val	Pro
		Glu 145	Ala	Ile	Gly	Phe	<b>As</b> p 150	Thr	Thr	Ser	Asp	Tyr 155	Lys	Gly	Lys	Pro	Leu 160
		Arg	Val	Сув	Met	Leu 165	Asn	Pro	Phe	Gln	Lys 170	Thr	Ala	Phe	Met	Phe 175	Tyr
35		Lys	Thr	Ala	Ala 180	Lys	Asp	Trp	Trp	Leu 185	Phe	Ala	Phe	Tyr	Phe 190	Сув	Leu
		Pro	Leu	Ala 195	Ile	Thr	Ala	Ile	Phe 200	Tyr	Thr	Leu	Met	Thr 205	Cys	Glu	Met
40		Leu	Arg 210	Lys	Lys	Ser	Gly	<b>Me</b> t 215	Gln	Ile	Ala	Leu	Asn 220		His	Leu	Lys
		Gln 225	Arg	Arg	Glu	Val	Ala 230		Thr	Val	Phe	Cys 235	Leu	Val	Leu	Val	Phe 240
		Ala	Leu	Cys	Trp	Leu 245		Leu	His	Leu	Ser 250	Arg	Ile	Leu	Lys	Leu 255	Thr
45		Leu	Tyr	qaA	Gln 260		Asn	Pro	Gln	<b>Arg</b> 265		Glu	Leu	Leu	Ser 270		Leu
		Leu	Val	Leu	Asp	Tyr	Ile	Gly	Ile	Asn	Met	Ala	Ser	Ile	naA	Ser	Cys

			275					280					285			
	Ile	Asn 290	Pro	Ile	Ala	Leu	Tyr 295	Leu	Val	Ser	Lys	Arg 300	Phe	Lys	Asn	Cys
5	Phe 305	Lys	Ser	Cys	Leu	Cys 310	Cys	Trp	Cys	Gln	Thr 315	Phe	Glu	Glu	Lys	Gln 320
	Ser	Leu	Glu	Glu	Lys 325	Gln	Ser	Cys	Leu	Lys 330	Phe	Lys	Ala	Asn	<b>Asp</b> 335	His
	Gly	Tyr	Asp	Asn 340	Phe	Arg	Ser	Ser	Asn 345	Lys	Tyr	Ser	Ser	Ser 350		
10	(2) INFO	SEQUAL (A)		E CHI NGTH: PE: & RANDI	ARAC 328 amino SDNES	reris 3 ami 5 aci 5S: 8	STICS ino a id singl	S: acids	5							
-5	(ii)	MOLI					_									
		SEQU Tyr									Ile	Ile	Val	Ile	Gly 15	Leu
20	Ile	Gly	Asn	Ile 20	Thr	Leu	Ile	Lys	Ile 25	Phe	Cys	Thr	Val	Tys	Ser	Leu
	Asn	Leu	Phe 35	Ile	Ser	Ser	Ile	Ala 40	Leu	Gly	Asp	Leu	Leu 45	Leu	Leu	Val
25	Thr	Ile 50	Cys	Ala	Pro	Val	<b>As</b> p 55	Ala	Ser	Lys	Tyr	Ile 60	Ala	ĄąĄ	Arg	Trp
	Leu 65	Phe	Gly	Arg	Ile	Gly 70	Cys	Lys	Leu	Ile	Pro 75	Phe	Ile	Gln	Leu	Thr 80
	Ser	Val	Gly	Val	Ser 85	Val	Phe	Thr	Leu	Thr 90	Ala	Leu	Ser	Ala	<b>As</b> p 95	Arg
30	Tyr	Lys	Ala	Ile 100	Val	Arg	Pro	Thr	Cys 105	Ile	Gln	Ala	Ser	Leu 110	Ile	Cys
	Leu	Lys	Ala 115	Ala	Leu	Ile	Trp	Ile 120	Val	Ser	Leu	Leu	Ala 125	Ile	Pro	Glu
35	Ala	Val 130	Phe	Ser	qaA	Leu	His 135	Pro	Phe	His	Val	Lys 140	qaA	Thr	Asn	Gln
	Thr 145	Phe	Ile	Ser	Cys	Ala 150	Pro	Tyr	Pro	His	Ser 155	Asn	Glu	Leu	His	Pro 160
	Lys	Ile	His	Ser	Met 165	Ala	Ser	Phe	Leu	Val 170	Phe	Tyr	Val	Ile	Pro 175	Leu
40	Ala	Ile	Ile	Ser 180	Val	Tyr	Tyr	Tyr	Phe 185	Ile	Ala	Arg	Asn	Leu 190	Ile	Gln
	Ser	Ala	Tyr 195	Asn	Leu	Pro	Val	Glu 200	Gly	Asn	Ile	His	Val 205	Lys	Lys	Gln
45	Ile	Glu 210	Ser	Arg	Lys	Arg	Leu 215	Ala	Lys	Thr	Val	<b>Le</b> u 220	Val	Phe	Val	Gly
	Leu 225	Phe	Ala	Phe	Cys	Trp 230	Leu	Pro	Asn	His	Val 235	Ile	Tyr	Leu	Tyr	Arg 240

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	Ser	Tyr	His	Tyr	Ser 245	Glu	Val	Asp	Thr	Ser 250	Met	Leu	His	Phe	Val 255	Thr
	Ser	Ile	Сув	Ala 260	Arg	Leu	Leu	Ala	Pro 265	Thr	Asn	Ser	Cys	Val 270	Asn	Pro
5	Phe	Ala	Leu 275	Tyr	Leu	Leu	Ser	Lys 280	Ser	Phe	Arg	Gln	Phe 285	Asn	Thr	Gln
	Leu	Leu 290	Cys	Сув	Gln	Pro	Gly 295	Leu	Ser	His	Ser	Thr 300	Gly	Arg	Ser	Leu
10	Ser 305	Phe	Lys	Ser	Thr	<b>Asn</b> 310	Pro	Ser	Ala	Thr	Phe 315	Ser	Leu	Ile	Asn	Arg 320
	Asn	Ile	Сув	His	Glu 325	Gly	Tyr	Val								
15	(2) INFOI (i)	SEQUAL (A) (B) (C) (D)	JENCH LEN TYI STI TOI	CHANGTH: PE: 6 RANDI POLOG	ARACT : 345 mind SDNES SY: 1	TERIS  ami  aci  SS: s  lines	STICS ino a id singl	S: acids	5							
20	(xi) Cys 1	_				PTION Ser		-			Ile	Ile	Ser	Val	Gly 15	Leu
	Leu	Gly	Asn	Ile 20	Met	Leu	Val	Lys	Ile 25	Phe	Leu	Thr	Asn	Ser 30	Thr	Met
25	Arg	Ser	<b>Val</b> 35	Pro	Asn	Ile	Phe	Ile 40	Ser	Asn	Ile	Ala	Ala 45	Gl <u>r</u>	qaA	Leu
	Leu	Leu 50	Leu	Leu	Thr	Сув	Val 55	Pro	Val	Asp	Ala	Ser 60	Arg	Tyr	Phe	Phe
30	65		_			Gly 70					75					80
	Ile	Gln	Leu	Thr	Ser 85	Val	Gly	Val	Ser	Val 90	Pro	Thr	Leu	Thr	Ala 95	Leu
	Ser	Ala	Asp	Arg 100	Tyr	Arg	Ala	Ile	Val 105	Asn	Pro	Met	Asp	Met 110	Thr	Ser
35	Gly	Val	<b>Val</b> 115	Leu	Trp	Thr	Ser	Val 120	Ala	Val	Gly	Ile	Trp 125	Val	Val	Ser
	Val	Leu 130	Leu	Ala	Val	Pro	Glu 135	Ala	Val	Phe	Ser	Glu 140	Val	Ala	Arg	Ile
40	Gly 145	Ser	Ser	qaA	Asn	Ser 150	Ser	Phe	Thr	Ala	Сув 155	Ile	Pro	Tyr	Pro	Gln 160
	Thr	Asp	Glu	Leu	His 165	Pro	Lys	Ile	His	Ser 170	Val	Leu	Ile	Phe	Leu 175	Val
	Tyr	Phe	Leu	Ile 180	Pro	Leu	Val	Ile	Ile 185	Ser	Ile	Tyr	Tyr	Ty_ 190	His	Ile
45	Ala	Lys	Thr 195	Leu	lle	Arg	Ser	Ala 200	His	Asn	Leu	Pro	Gly 205	Glu	Tyr	Asn
	Glu	His	Thr	Lys	Lys	Gln	Met	Glu	Thr	Arg	Lys	Arg	Leu	Ala	Lys	Ile

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			210					215					220				
		Val 225	Leu	Val	Phe	Val	Gly 230	Сув	Phe	Val	Phe	Cys 235	Trp	Phe	Pro	Asn	His 240
5		Ile	Leu	Tyr	Leu	Tyr 245	Arg	Ser	Phe	Asn	Tyr 250	Lys	Glu	Ile	Asp	Pro 255	Ser
		Leu	Gly	Thr	Cys 260	Val	Thr	Leu	Val	Ala 265	Arg	Val	Leu	Ser	Phe 270	Ser	Asn
		Ser	Cys	<b>Val</b> 275	Asn	Pro	Phe	Ala	Leu 280	Tyr	Leu	Leu	Ser	Glu 285	Ser	Phe	Arg
10		Lys	His 290	Phe	Ser	Asn	Gln	Leu 295	Суѕ	Cys	Gly	Gln	Lys 300	Ser	Tyr	Pro	Glu
		Arg 305	Ser	Thr	Ser	Tyr	Leu 310	Leu	Ser	Ser	Ser	Ala 315	Val	Trp	Arg	Ser	Leu 320
15		Lys	Ser	Asn	Ala	Lув 325	Asn	Val	Val	Thr	Asn 330	Ser	Val	Leu	Ile	<b>Asn</b> 335	Gly
		His	Ser	Thr	Lys 340	Gln	Glu	Ile	Ala	Leu 345							
20	(2)	(i)	SEQUAL (A)	JENCI LEI TYI STI	CHANGTH PE: 6 RANDI		TERIS 5 am: 5 ac: 5S: 5	TICS ino a id sing	S: acida	5							
		(ii)	MOT.	enn.	TY	PE: p	ept:	ide									
		,,	11011														
25		(xi)	SEQ	JENCI	E DES	SCRII	TIO	1: SI	EQ II Ile	NO Phe	:44: Ile 10	Phe	Val	Ile	Cys	Glx 15	Leu
25		(xi) Tyr 1	SEQI Thr	JENCI Leu	E DES Ser	SCRII Phe 5	PTIOI Ile	N: SI Tyr	Ile	Phe	Ile 10						
25 30		(xi) Tyr 1 Leu	SEQI Thr	JENCI Leu Asn	Ser Ser 20	SCRII Phe 5 Val	PTION Ile Val	N: SI Tyr Val	Ile	Phe Val 25	Ile 10 Asn	Ile	Gln	Ala	Lys 30	15 Thr	
		(xi) Tyr 1 Leu Gly	SEQU Thr Ala	JENCI Leu Asn Asp 35	Ser Ser 20	SCRII Phe 5 Val	PTIOI Ile Val	N: SI Tyr Val Tyr	Trp	Val 25 Leu	Ile 10 Asn Asn	Ile Leu	Gln Ala	Ala Ile 45	Lys 30 Ala	Thr Asp	Thr
		(xi) Tyr 1 Leu Gly Trp Trp 65	SEQUENT THE TYPE TO THE TYPE TYPE TO THE TYPE TYPE TYPE TYPE TYPE TYPE TYPE TYP	JENCI Leu Asn Asp 35 Leu Met	Ser Ser 20 Thr Thr	SCRII Phe 5 Val His Ile	PTION Ile Val Cys Pro Leu 70	Val Tyr Val Val 55	Trp Ile 40 Trp Cys	Val 25 Leu Trp	Ile 10 Asn Asn Ser Val	Ile Leu Leu Thr	Gln Ala Val 60 His	Ala Ile 45 Gln Leu	Lys 30 Ala His	Thr Asp Asn Phe	Thr Leu Gln Ser 80
30		(xi) Tyr 1 Leu Gly Trp Trp 65	SEQUENT THE TYPE TO THE TYPE TYPE TO THE TYPE TYPE TYPE TYPE TYPE TYPE TYPE TYP	JENCI Leu Asn Asp 35 Leu Met	Ser Ser 20 Thr Thr	SCRII Phe 5 Val His Ile	PTION Ile Val Cys Pro Leu 70	Val Tyr Val Val 55	Trp Ile 40 Trp Cys	Val 25 Leu Trp	Ile 10 Asn Asn Ser Val	Ile Leu Leu Thr	Gln Ala Val 60 His	Ala Ile 45 Gln Leu	Lys 30 Ala His	Thr Asp Asn	Thr Leu Gln Ser 80
30		(xi) Tyr 1 Leu Gly Trp Trp 65 Ile	SEQUENT THE Ala Tyr Trp 50 Pro	Asn Asp 35 Leu Met	Ser Ser 20 Thr Thr Gly	SCRII Phe 5 Val His Ile Glu Ser 85	PTION Ile  Val  Cys  Pro  Leu 70  Gly	Val Tyr Val Tyr Val 55 Thr	Trp Ile 40 Trp Cys	Val 25 Leu Trp Lys	Ile 10 Asn Asn Ser Val Leu 90	Ile Leu Leu Thr 75 Thr	Gln Ala Val 60 His	Ala Ile 45 Gln Leu Met	Lys 30 Ala His Ile Ser	Thr Asp Asn Phe Val	Thr Leu Gln Ser 80 Asp
30		(xi) Tyr 1 Leu Gly Trp Trp 65 Ile Arg	SEQUENT THE Ala Tyr Trp 50 Pro Asn Tyr Met	Asn Asp 35 Leu Met Leu Val	Ser 20 Thr Thr Gly Phe Ser 100 Arg	CCRII Phe 5 Val His Ile Glu Ser 85 Ile	PTION Ile Val Cys Pro Leu 70 Gly Thr	Val Tyr Val Thr Ile Tyr Val	Trp Ile 40 Trp Cys Phe Phe Cys 120	Phe Val 25 Leu Trp Lys Phe Thr 105	Asn Asn Ser Val Leu 90 Asn Leu	Ile Leu Leu Thr 75 Thr Val	Gln Ala Val 60 His Cys Pro	Ala Ile 45 Gln Leu Met Ser Leu 125	Lys 30 Ala His Ile Ser Sei 110 Leu	Thr Asp Asn Phe Val 95 Arg	Thr Leu Gln Ser 80 Asp Lys
30		(xi) Tyr 1 Leu Gly Trp Trp 65 Ile Arg	SEQUENT THE Ala Tyr Trp 50 Pro Asn Tyr Met	Asn Asp 35 Leu Met Leu Val	Ser 20 Thr Thr Gly Phe Ser 100 Arg	CCRII Phe 5 Val His Ile Glu Ser 85 Ile	PTION Ile Val Cys Pro Leu 70 Gly Thr	Val Tyr Val Thr Ile Tyr Val	Trp Ile 40 Trp Cys Phe Phe Cys 120	Phe Val 25 Leu Trp Lys Phe Thr 105	Asn Asn Ser Val Leu 90 Asn Leu	Ile Leu Leu Thr 75 Thr Val	Gln Ala Val 60 His Cys Pro	Ala Ile 45 Gln Leu Met Ser Leu 125	Lys 30 Ala His Ile Ser Sei 110 Leu	Thr Asp Asn Phe Val 95 Arg	Thr Leu Gln Ser 80 Asp
30		(xi) Tyr 1 Leu Gly Trp 65 Ile Arg Lys Cys Ser 145	SEQUENT Tryr Ala Tyr Trp 50 Pro Asn Tyr Met Val 130 Asn	Asn Asp 35 Leu Met Leu Val 115 Ser Asn	Ser 20 Thr Thr Gly Phe Ser 100 Arg Leu Glu	CCRII Phe 5 Val His Ile Glu Ser 85 Ile Arg Pro	PTION Ile Val Cys Pro Leu 70 Gly Thr Ala Asp	Val Tyr Val Tyr Ile Tyr Val Tyr Cys	Trp Ile 40 Trp Cys Phe Phe Cys 120 Tyr Arg	Phe Val 25 Leu Trp Lys Phe Thr 105 Ile Tyr	Asn Asn Ser Val Leu 90 Asn Leu Phe	Ile Leu Thr 75 Thr Thr Val Lys	Gln Ala Val 60 His Cys Pro Trp Thr 140 Pro	Ala Ile 45 Gln Leu Met Ser Leu 125 Val	Lys 30 Ala His Ile Ser Se: 110 Leu Thr	Thr Asp Asn Phe Val 95 Arg Ala Ser	Thr Leu Gln Ser 80 Asp Lys Phe Ala Ile 160

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		Ala	Val	Pro	Phe 180	Ser	Ile	Ile	Ala	Val 185	Phe	Tyr	Phe	Ser	L∈u 190	Ile	Ala
		Arg	Ala	Ile 195	Ser	Ala	Ser	Ser	Asp 200	Gln	Glu	Lys	His	Ser 205	Ser	Arg	Lys
5		Ile	Ile 210	Phe	Ser	Tyr	Val	Val 215	Val	Phe	Leu	Val	Cys 220	Trp	Leu	Pro	Tyr
		His 225	Val	Ala	Val	Leu	Leu 230	Asp	Ile	Phe	Ser	Ile 235	Leu	His	Tyr	Ile	Pro 240
10		Phe	Thr	Сув	Arg	Leu 245	Glu	His	Ala	Leu	Phe 250	Thr	Ala	Leu	His	Val 255	Thr
		Gln	Сув	Leu	Ser 260	Leu	Val	His	Сув	Cys 265	Val	Asn	Pro	Val	Leu 270	Tyr	Ser
		Phe	Ile	Asn 275	Arg	Asn	Tyr	Arg	Tyr 280	Glu	Ile	naA	Trp	Ile 285	Phe	Lys	Tyr
15		Ser	Ala 290	Lys	Thr	Gly	Leu	Thr 295	Lys	Leu	Ile	Asp	Ala 300	Ser	Arg	Val	Ser
		Glx 305	Thr	Glu	Tyr	Ser	Ala 310	Leu	Glu	Gln	Asn	Ala 315	Lys				
20	(2)	INFOI (i)	SEQUAL (A)	JENCI LEI TYI	CHINGTH	ARĀC : 35: amin	ID NO PERIS 3 am: 5 ac:	STIC: ino a id	S: acida	5							
			(D)	ו יייי	POT O	7V . '	linea	ar .									
25		(ii)															
25		(xi)	MOL	ECULI UENCI	E DE	PE: 1 SCRI		ide N:S				Leu	Phe	Val	Va:	Gly 15	Thr
<b>25</b> <b>30</b>		(xi) Lys 1	MOLI SEQU Val	ECULI UENCI Leu	E TY: E DE: Val	PE: ] SCRI: Thr 5	PEPT: PTION Ala	ide N: S: Ile	Tyr	Leu	Ala 10					15	Thr Leu
		(xi) Lys 1 Val	MOLI SEQU Val	ECULI UENCI Leu Asn	E TYN E DE: Val Ser 20	PE: ] SCRI: Thr 5 Val	PTION Ala Thr	ide N: S: Ile Ala	Tyr	Leu Thr 25	Ala 10 Leu	Ala	Arg	Lys	Lys 30	15 Ser	
		(xi) Lys 1 Val Gln	MOLI SEQU Val Gly Ser	Leu 35	E TYN E DE: Val Ser 20	SCRIE Thr 5 Val	PTION Ala Thr	ide N: S: Ile Ala Val	Tyr Phe His	Thr 25 Tyr	Ala 10 Leu His	Ala Leu	Arg Ser	Lys Ser 45	Lys 30 Leu	Ser	Leu
		(xi) Lys 1 Val Gln	MOLD SEQUENCE Gly Ser Asp 50	Leu 35 Leu	E TYN E DE: Val Ser 20 Gln Leu	SCRI: Thr 5 Val Ser	PTION Ala Thr Thr	ide N: S: Ile Ala Val Leu 55	Tyr Phe His 40 Trp	Thr 25 Tyr Val	Ala 10 Leu His	Ala Leu Leu	Arg Ser Tyr 60	Lys Ser 45 Asn	Lys 30 Leu Phe	Ser Ala Ile	Leu Leu
30		(xi) Lys 1 Val Gln Ser His	SEQUENCY SET  Asp 50  His	Leu Asn Leu 35 Leu Pro	Ser 20 Gln Leu	PE: property of the service of the s	PTION Ala Thr Thr Leu Phe	ide N: Si Ile Ala Val Leu 55	Tyr Phe His 40 Trp Asp	Thr 25 Tyr Val	Ala 10 Leu His Glu	Ala Leu Leu Cys 75	Arg Ser Tyr 60 Arg	Lys Ser 45 Asn Gly	Lys 30 Leu Phe	Ser Ala Ile Tyr	Leu Leu Trp Phe
30		(xi) Lys 1 Val Gln Ser His 65 Leu	MOLD SEQUENCE Gly Ser Asp 50 His	Leu Asn Leu 35 Leu Pro	Ser 20 Gln Leu Trp	PE: PESCRIENTS Thr 5 Val Ser Ile Ala Cys 85	PTION Ala Thr Thr Leu Phe 70 Thr	ide N: S: Ile Ala Val Leu 55 Gly	Tyr Phe His 40 Trp Asp	Thr 25 Tyr Val Ala Thr	Ala 10 Leu His Glu Gly Ala 90	Ala Leu Leu Cys 75 Leu	Arg Ser Tyr 60 Arg	Lys Ser 45 Asn Gly Val	Lys 30 Leu Phe Tyr	Ser Ala Ile Tyr Ser 95 Lys	Leu Leu Trp Phe
30 35		(xi) Lys 1 Val Gln Ser His 65 Leu Ser	SEQUENCY SET  Asp 50  His  Arg	Leu Asn Leu 35 Leu Pro Asp	E TYN E DE: Val  Ser 20 Gln Leu Trp Ala Arg 100 Arg	PE:	PTION Ala Thr Thr Leu Phe 70 Thr Leu	ide N: S: Ile Ala Val Leu 55 Gly Tyr	Tyr Phe His 40 Trp Asp Ala	Thr 25 Tyr Val Ala Thr Cys 105 Lys	Ala 10 Leu His Glu Gly Ala 90 His	Ala Leu Leu Cys 75 Leu Pro	Arg Ser Tyr 60 Arg Asn	Lys Ser 45 Asn Gly Val	Lys 30 Leu Phe Tyr Ala Ala 110	Ser Ala Ile Tyr Ser 95 Lys	Leu Trp Phe 80 Leu
30 35		(xi) Lys 1 Val Gln Ser His 65 Leu Ser	MOLD SEQUENCE Gly Ser Asp 50 His Arg Val	Leu Asn Leu 35 Leu Pro Asp Glu Ser 115	Ser 20 Gln Leu Trp Ala Arg	PE:	PTION Ala Thr Thr Leu Phe 70 Thr Leu Arg	ide N: S: Ile Ala Val Leu 55 Gly Tyr Ala	Phe His 40 Trp Asp Ala Ile Lys 120 Pro	Thr 25 Tyr Val Ala Thr Cys 105 Lys	Ala 10 Leu His Glu Gly Ala 90 His	Ala Leu Leu Cys 75 Leu Pro	Arg Ser Tyr 60 Arg Asn Phe	Lys Ser 45 Asn Gly Val Lys Ala 125	Lys 30 Leu Phe Tyr Ala Ala 110	Ser Ala Ile Tyr Ser 95 Lys Trp	Leu Trp Phe 80 Leu Thr
30 35		(xi) Lys 1 Val Gln Ser His 65 Leu Ser Leu Ala	MOLD SEQUENCE OF SECUENCE OF S	Leu Asn Leu 35 Leu Pro Asp Glu Serr 115	E TYN E DE: Val  Ser 20 Gln Leu Trp Ala Arg 100 Arg	PE:	PTION Ala Thr Thr Leu Phe 70 Thr Leu Arg	ide N: S: Ile Ala Val Leu 55 Gly Tyr Ala Thr Ile 135	Phe His 40 Trp Asp Ala Ile Lys 120 Pro	Thr 25 Tyr Val Ala Thr Cys 105 Lys	Ala 10 Leu His Glu Gly Ala 90 His Phe	Ala Leu Leu Cys 75 Leu Pro Ile	Arg Ser Tyr 60 Arg Asn Phe Ser Thr 140 Leu	Lys Ser 45 Asn Gly Val Lys Ala 125 Leu	Lys 30 Leu Phe Tyr Ala 110 Ile	Ser Ala Ile Tyr Ser 95 Lys Trp Leu	Leu Trp Phe 80 Leu Thr

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						165					170					175	
		Met	Ser	Phe	Leu 180	Phe	Pro	Met	Leu	Val 185	Ile	Ser	Ile	Leu	Asn 190	Thr	۷al
5		Ile	Ala	<b>Asn</b> 195	Lys	Leu	Thr	Val	<b>Met</b> 200	Val	His	Gln	Ala	Ala 205	Glu	Gln	Gly
		Arg	Val 210	Cys	Thr	Val	Gly	Thr 215	His	Asn	Gly	Leu	Glu 220	His	Ser	Thr	Ph€
		Asn 225	Met	Arg	Ile	Glu	Pro 230	Gly	Arg	Val	Gln	Ala 235	Leu	Arg	His	Gly	Va] 24(
LO		Leu	Val	Leu	Arg	Ala 245	Val	Val	Ile	Ala	Phe 250	Val	Val	Сув	Trp	Leu 255	Pro
		Tyr	Leu	Cys	Тут 260	Ile	Ser	Asp	Glu	Gln 265	Trp	Arg	Thr	Phe	Leu 270	Phe	Asp
L5			-	275	_		_		280					285		Val	
		Ser	Ala 290	Ile	Asn	Pro	Ile	Leu 295	Tyr	Asn	Leu	Val	Ser 300	Ala	Asn	Phe	Arg
		305					310			_		315				Trp	320
20						325					330					Asn 335	
		_	Ser	Ser	Asn 340	His	Ala	Phe	Ser	Thr 345	Ser	Ala	Thr	Arg	9he 350	Thr	Let
25		Tyr															
30	(2)	(i)	SEQUAL (A)	JENCI LEI TYI STI	E CHI NGTH PE: & RANDI	ARAC: : 310 amino EDNE:	TERIS 5 am: 5 ac: 5S: 1	STICS ino a id sing:	S: acids	5							
		(ii)			POLO(												
35		(xi) Ala 1										Phe	Leu	Leu	Ala	Ala 15	Let
		Glu	Asn	Ile	Phe 20	Val	Leu	Ser	Val	Phe 25	Cys	Leu	His	Lys	Thr 30	Asn	Cys
		Thr	Val	Ala 35	Glu	Ile	Tyr	Leu	Gly 40	Asn	Ile	Ala	Ser	Ala 45	Asp	Leu	Ile
10		Ile	Ala 50	Cys	Gly	Leu	Pro	Phe 55	Trp	Ala	Ile	Thr	Ile 60	Ala	Asn	Asn	Phe
		Asp 65	Trp	Leu	Phe	Gly	Glu 70	Val	Leu	Суѕ	Arg	Val 75	Val	Asn	Leu	Tyr	<b>M</b> et 80
<b>4</b> 5		Asn	Leu	Tyr	Ser	Ser 85	Ile	Суѕ	Phe	Leu	Val 90	Ser	Ile	Asp	Arq	Tyr 95	Let
		Ala	Leu	Val	Lys 100	Thr	Met	Ser	Asn	Leu 105	Arg	Trp	Ala	Lys	Leu 110	Tyr	Set

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	Leu	Val	Ile 115	Trp	Ser	Cys	Thr	Leu 120	Leu	Leu	Ser	Ser	Pro 125	Met	Leu	Val
	Phe	Arg 130	Thr	Met	Tyr	Arg	Glu 135	Glu	Gly	His	Asn	Val 140	Thr	Суы	Val	Ile
5	Val 145	Tyr	Pro	Ser	Arg	Ser 150	Trp	Glu	Val	Phe	Leu 155	Leu	Asn	Leu	Val	Gly 160
	Phe	Leu	Leu	Pro	Leu 165	Ser	Ile	Ile	Thr	Phe 170	Cys	Thr	Val	Arg	Ile 175	Met
10	Val	Leu	Arg	Asn 180	Asn	Glu	Met	Lys	Lys 185	Phe	Lys	Glu	Val	Gln 190	Thr	Glu
	Lys	Lys	Ala 195	Thr	Val	Leu	Val	Ile 200	Ala	Val	Leu	Gly	Leu 205	Phe	Val	Leu
	Cys	Trp 210	Phe	Pro	Phe	Gln	Ile 215	Ser	Thr	Phe	Leu	Asp 220	Thr	Leu	Leu	Arg
15	Leu 225	Gly	Val	Leu	Ser	Gly 230	Cys	Trp	Asn	Glu	Arg 235	Ala	Val	Asp	Ile	Val 240
	Arg	Gln	Ile	Ser	Ser 245	Tyr	Val	Ala	Tyr	Ser 250	Asn	Ser	Суѕ	Leu	Asn 255	Pro
20	Leu	Val	Tyr	Val 260	Ile	Val	Gly	Lys	Arg 265	Phe	Arg	Lys	Lys	Ser 270	Arg	Glu
	Val	Tyr	Gln 275	Ala	Ile	Cys	Arg	Lys 280	Gly	Gly	Сув	Met	Gly 285	Glu	Ser	Val
	Leu	Asn 290	Ser	Met	Gly	Thr	Leu 295	Arg	Thr	Ser	Ile	Ser 300	Val	qaA	Arg	Gln
25	Ile 305	His	Lys	Leu	Gln	Asp 310	Trp	Ala	Gly	Asn	Lys 315	Gln				
30	(i)	(B)	JENCE LEI TYI STI	E CHA NGTH: PE: & RANDE POLOC	RACT 347 mino DNES Y: ]	TERIS ami aci SS: s linea	STICS ino a id singl	3: acids	3							
35	Ile	SEQU Leu			Val					Leu	Gly	Ile	Val	Gl;		Ile
	1 Met	Val	Val		5 Val	Val	Met	Arg		10 Thr	Pro	Thr	Asn	Сув	15 Tyr	Leu
40	Val	Ser	Ile 35	20 Ala	Val	Ala	Asp	Leu 40	25 Met	Val	Leu	Val	Ala 45	30 Ala	Gly	Leu
	Pro	<b>As</b> n 50		Thr	Asp	Ser	Ile 55		Gly	Ser	Trp	Val 60		Gly	Tyr	Val
	Gly 65	Cys	Leu	Cys	Ile	Thr 70	Tyr	Leu	Gln	Tyr	Leu 75	Gly	Ile	Asn	Ala	Ser 80
45	Ser	Суѕ	Ser	Ile	Thr 85	Ala	Phe	Thr	Ile	Glu 90	Arg	Tyr	Ile	Ala	Ile 95	Cys
	His	Pro	Ile	Lys	Ala	Gln	Phe	Leu	Cys	Thr	Phe	Ser	Arg	Ala	Lys	Lys

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					100					105					110		
		Ile	Ile	Ile 115	Phe	Val	Trp	Ala	Phe 120	Thr	Ser	Ile	Tyr	Leu 125	Phe	Leu	Leu
5		Asp	Ile 130	Asn	Ile	Ser	Thr	Tyr 135	Lys	Asn	Ala	Val	Val 140	Val	Ser	Cys	Gly
		Tyr 145	Lys	Ile	Ser	Arg	Asn 150	Tyr	Tyr	Ser	Pro	Ile 155	Tyr	Leu	Met	Asp	Phe
		Gly	Val	Phe	Tyr	Val 165	Val	Pro	Leu	Ile	Ala 170	Thr	Val	Leu	Tyr	Gly 175	Phe
LO		Ile	Ala	Arg	Ile 180	Leu	Phe	Leu	Asn	Pro 185	Ile	Pro	Ser	Asp	Pro 190	Lys	Glu
		Asn	Ser	Lys 195	Met	Trp	Lys	Asn	Asp 200	Ser	Ile	His	Gln	Asn 205	Lys	Asn	Leu
15		Asn	Leu 210	Asn	Ala	Ser	Ser	Arg 215	Lys	Gln	Val	Thr	Ile 220	Asn	Leu	Ala	Val
		Val 225	Val	Ile	Leu	Phe	Ala 230	Leu	Leu	Trp	Asn	Thr 235	Tyr	Arg	Thr	Leu	Val 240
		Val	Val	Asn	Ser	Phe 245	Leu	Ser	Ser	Pro	Phe 250	Gln	Glu	Asn	Trp	Lys 255	Leu
20		Leu	Lys	Cys	Arg 260	Ile	Сув	Ile	Tyr	Leu 265	Asn	Ser	Ala	Ile	Asn 270	Pro	Val
		Ile	Tyr	Asn 275	Ile	Met	Ser	Gln	Lys 280	Arg	Phe	Ala	Ala	Phe 285	Arg	Lys	Leu
25		Cys	Asn 290	Cys	Lys	Gln	Lys	Pro 295	Tḥr	Glu	Lys	Ala	Ala 300	Asn	Tyr	Ser	Val
		Ala 305	Leu	Asn	Tyr	Ser	Val 310	Ile	Lys	Glu	Ser	<b>Asp</b> 315	Arg	Phe	Ser	Thr	Glu 320
		Leu	Glu	Asp	Ile	Thr 325	Val	Thr	Asp	Thr	Tyr 330	Val	Ser	Thr	Thr	Lys 335	Val
30		Ser	Phe	Asp	Asp 340	Thr	Cys	Ile	Ala	Ser 345	Glu	Asn					
	(2)	INFO	TAMS	ION I	FOR S	SEQ :	ID N	D:48	:								
35		(i)	(A) (B) (C)	JENCI ) LEI ) TYI ) STI ) TOI	NGTH PE: 8 RANDI	: 34: amino EDNE:	lam: cac: SS: s	ino a id sing:	acid	5							
		(ii)															
<b>1</b> 0		(xi) Leu 1		JENCI Leu								Leu	Val	Leu	Va.	Ala 15	Val
		Thr	Gly	Asn	Ala 20	Ile	Val	Ile	Trp	Ile 25	Ile	Leu	Ala	His	Arg 30	Arg	Met
<b>4</b> 5		Arg	Thr	Val 35	Thr	Asn	Tyr	Phe	Ile 40	Val	Asn	Ile	Ala	Leu 45	Ala	Asp	Let
		Leu	Asn	Ala	Ala	Phe	Asn	Phe	Val	Tvr	Ala	Ser	His	Asn	Ile	Trp	Tvr

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			50					55					60				
		Phe 65	Gly	Arg	Ala	Phe	Cys 70	Tyr	Phe	Gln	Asn	Leu 75	Phe	Pro	Ile	Thr	Ala 80
5		Met	Phe	Val	Ser	Ile 85	Tyr	Ser	Met	Thr	Ala 90	Ile	Ala	Ala	Asp	Arg 95	Tyr
		Met	Ala	Ile	Val 100	His	Pro	Phe	Gln	Pro 105	Arg	Leu	Ser	Ala	Pro 110	Ser	Thr
		Lys	Ala	Val 115	Ile	Ala	Gly	Ile	Trp 120	Leu	Val	Ala	Ile	Lys 125	Leu	Ala	Phe
10		Pro	Gln 130	Сув	Phe	Tyr	Ser	Thr 135	Val	Thr	Met	Gln	Gly 140	Ala	Thr	Lys	Cys
		Val 145	Val	Ala	Trp	Pro	Glu 150	Asp	Ser	Gly	Gly	Lys 155	Thr	Leu	Leu	Leu	Tyr 160
15		His	Leu	Val	Val	Ile 165	Ala	Leu	Ile	Tyr	Phe 170	Leu	Pro	Ile	Ala	Leu 175	Ala
		Tyr	Ser	Val	Ile 180	Gly	Leu	Thr	Leu	Trp 185	Arg	Arg	Ala	Val	Pro 190	Gly	His
		Gln	Ala	His 195	Gly	Ala	Asn	Leu	Arg 200	His	Leu	Gln	Ala	<b>Lys</b> 205	Lyś	Lys	Phe
20		Val	Lys 210	Thr	Met	Val	Leu	<b>Val</b> 215	Val	Val	Thr	Phe	Ala 220	Ile	Суѕ	Trp	Leu
		Pro 225	Tyr	His	Leu	Tyr	Phe 230	Ile	Leu	Gly	Ser	Phe 235	Gln	Glu	Asp	Ile	Tyr 240
25		Cys	His	Lys	Phe	Ile 245	Gln	Gln	Val	Tyr	Leu 250	Ala	Leu	Phe	Trp	Leu 255	Ala
		Met	Ser	Ser	Thr 260	Met	Tyr	Asn	Pro	Ile 265	Ile	Tyr	Cys	Cys	Leu 270	Asn	His
		Arg	Phe	<b>Arg</b> 275	Ser	Gly	Phe	Arg	Leu 280	Ala	Phe	Arg	Сув	Cys 285	Pro	Trp	Val
30		Thr	Pro 290	Thr	Lys	Glu	Asp	Lys 295	Leu	Glu	Leu	Thr	Pro 300	Thr	Thr	Ser	Leu
		Ser 305	Thr	Arg	Val	Asn	Arg 310	Суѕ	His	Thr	Lys	Glu 315	Thr	Leu	Phe	Met	Ala 320
35		Gly	Asp	Thr	Ala	Pro 325	Ser	Glu	Ala	Thr	Ser 330	Gly	Glu	Ala	Gly	<b>A</b> rg 335	Pro
		Gln	Asp	Gly	Ser 340	Gly											
40	(2)	(ii)	SEQT (A) (B) (C) (D)	JENCI LEI TYI STI	E CHI NGTH PE: 6 RANDI POLO	ARACT : 340 emino EDNES GY:	reris o am: o ac: ss: s linea	STICS ino a id sing: ar	S: acids	5							
45		(xi)	SEQ	JENCI		SCRI	PTIO	N: SI				Ile	Val	Val	Arg	Ser	Val

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	Val	Gly	Asn	Val 20	Val	Val	Ile	Trp	Ile 25	Ile	Leu	Ala	His	Lys 30	Arg	Met
	Arg	Thr	Val 35	Thr	Asn	Tyr	Phe	Leu 40	Val	Asn	Ile	Ala	Phe 45	Ala	Phe	Ala
5	Leu	Asn 50	Thr	Trp	Asn	Phe	Thr 55	Tyr	Ala	Val	His	Asn 60	Val	Trp	Tyr	Tyr
	Gly 65	Leu	Phe	Tyr	Сув	Lys 70	Phe	His	Asn	Phe	Phe 75	Pro	Ile	Ala	Ala	Leu 80
10	Phe	Ala	Ser	Ile	Tyr 85	Ser	Met	Thr	Ala	Val 90	Ala	Phe	qaA	Arg	Tyr 95	Leu
	Ile	Ile	His	Pro 100	Leu	Gln	Pro	Arg	Leu 105	Ser	Ala	Thr	Ala	Thr 110	Lys	Val
	Val	Ile	Phe 115	Val	Ile	Trp	Val	Ile 120	Ala	Leu	Leu	Leu	Ala 125	Ser	Pro	Gln
15	Gly	Tyr 130	Tyr	Ser	Thr	Thr	Glu 135	Leu	Ser	Arg	Val	Val 140	Cys	Met	Ile	Glu
	Trp 145	Pro	Glu	His	Pro	Asn 150	Arg	Thr	Tyr	Glu	Lys 155	Ala	Tyr	Hi⊊	Ile	Cys 160
20	Val	Thr	Val	Leu	Ile 165	Tyr	Phe	Leu	Pro	Leu 170	Leu	Val	Ile	Gly	Tyr 175	Ala
	Tyr	Thr	Val	Val 180	Gly	Ile	Thr	Leu	Trp 185	Ala	Ser	Glu	Ile	Pro 190	Gly	Asp
	Ser	Ser	Asp 195	Arg	Tyr	His	Glu	Gln 200	Val	Ser	Ala	Lys	Arg 205	Lув	Val	Val
25	Lys	Met 210	Ile	Cys	Val	Val	Val 215	Cys	Thr	Phe	Ala	Ile 220	Cys	Trp	Leu	Pro
	Phe 225	His	Val	Phe	Phe	Leu 230	Leu	Pro	Tyr	Ile	Asn 235	Pro	Asp	Leu	Tyr	Leu 240
30	Lys	Lys	Phe	Ile	Gln 245	Gln	Val	Tyr	Ile	Ala 250	Ser	Met	Trp	Leu	Ala 255	Met
	Ser	Ser	Thr	<b>Met</b> 260	Tyr	Asn	Pro	Ile	11e 265	Tyr	Сув	Сув	Leu	Asn 270	Asp	Arg
	Phe	Arg	Leu 275	Gly	Phe	Lys	His	Ala 280	Phe	Arg	Cys	Cys	Pro 285	Phe	Ile	Ser
<b>3</b> 5	Ala	Gly 290	Asp	Tyr	Glu	Gly	Leu 295	Glu	Met	Ile	Lys	Ser 300	Thr	Arg	Tyr	Leu
	Gln 305	Thr	Leu	Ser	Ser	Val 310	Tyr	Lys	Val	Ser	Arg 315	Leu	Glu	Thr	Thr	Ile 320
40	Ser	Thr	Val	Val	Gly 325	Ala	His	Glu	Glu	Glu 330	Pro	Glu	Glu	Gly	Pro 335	Lys
	Ala	Thr	Pro	Ser 340												

## (2) INFORMATION FOR SEQ ID NO:50: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 336 amino acids (B) TYPE: amino acid

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(C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:50: 5 Ile Ala Leu Trp Ser Leu Ala Tyr Gly Leu Val Val Ala Val Ala Val Phe Gly Asn Leu Ile Val Ile Trp Ile Ile Leu Ala His Lys Arg Met Arg Thr Val Thr Asn Tyr Phe Leu Val Asn Leu Ala Phe Ser Asp Ala 10 Ser Val Ala Ala Phe Asn Thr Leu Ile Asn Phe Ile Tyr Gly Leu His Ser Glu Trp Tyr Phe Gly Ala Asn Tyr Cys Arg Phe Gln Asn Phe Phe 15 Pro Ile Thr Ala Val Phe Ala Ser Ile Tyr Ser Met Ala Ile Ala Val Asp Arg Tyr Met Ala Ile Ile Asp Pro Leu Lys Pro Arg Leu Ser Ala Thr Ala Thr Lys Ile Val Ile Gly Ser Ile Trp Ile Leu Ala Phe Leu 20 Leu Ala Phe Pro Gln Cys Leu Tyr Ser Lys Ile Leu Gly Arg Thr Leu Cys Tyr Val Trp Pro Glu Gly Pro Lys Gln His Phe Thr Tyr His Ile 25 Ile Val Ile Ile Leu Val Tyr Cys Phe Pro Leu Leu Ile Leu Thr Tyr Thr Ile Val Gly Ile Thr Leu Trp Gly Gly Glu Ile Pro Gly Asp Thr Cys Asp Lys Tyr His Glu Gln Leu Lys Ala Lys Arg Lys Val Val Met 30 Asn Ile Val Val Thr Phe Ala Ile Cys Trp Leu Pro Tyr His Val Tyr Phe Ile Leu Thr Ala Ile Tyr Gln Gln Leu Asn Arg Trp Lys Tyr 35 Ile Gln Gln Val Tyr Leu Ala Ser Phe Trp Leu Ala Met Ser Ser Thr Met Tyr Asn Pro Ile Ile Tyr Cys Cys Leu Asn Lys Arg Phe Arg Ala Gly Phe Lys Arg Ala Phe Arg Trp Cys Pro Phe Ile Gln Val Ser Ser 40 280 Tyr Asp Glu Leu Glu Leu Lys Thr Thr Arg Phe His Pro Thr Arg Gln Ser Ser Leu Tyr Thr Val Ser Phe Met Ser Val Thr Val Leu Phe Asp 45 Pro Asn Asp Gly Asp Pro Thr Lys Ser Ser Arg Lys Lys Arg Ala Val

330

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5	(2)		SEQUENT (A)	JENCI LEI TYI STI	E CHA NGTH PE: 8 RANDI POLO	ARAC: 32! emino EDNE: 3Y:	TERIS  am: cac: SS: s  lines	STICS ino a id sing: ar	S: acida	5							
10		(xi) Met 1										Val	Val	Gly	Ile	Phe 15	Gly
		Asn	Ser	Leu	<b>Val</b> 20	Val	Ile	Val	Ile	Tyr 25	Phe	Tyr	Met	Lys	Leu 30	Lys	Thr
		Tyr	Ala	Ser 35	Val	Phe	Leu	Leu	Asn 40	Leu	Ala	Leu	Ala	Asp 45	Leu	Cys	Phe
15		Leu	Leu 50	Thr	Leu	Pro	Leu	Trp 55	Ala	Val	Tyr	Thr	Leu 60	Tyr	Arg	Trp	Pro
		Phe 65	Gly	Asn	Tyr	Leu	Cys 70	Lys	Ile	Ala	Ser	Ala 75	Ser	Val	Ser	Phe	Asn 80
20		Leu	Tyr	Ala	Ser	Val 85	Phe	Leu	Leu	Thr	Cys 90	Leu	Ser	Ile	Asp	Arg 95	Tyr
		Leu	Ala	Ile	Val 100	His	Pro	Met	Lys	Ser 105	Arg	Leu	Arg	Arg	Leu 110	Val	Ala
		Lys	Val	Thr 115	Cys	Ile	Ile	Ile	Trp 120	Leu	Leu	Ala	Gly	Ile 125	Ala	Ser	Leu
25		Pro	Thr 130	Ile	Ile	His	Arg	Asn 135	Phe	Phe	Ile	Glu	Asn 140	Thr	Asn	Ile	Thr
		Val 145	Cys	Ala	Phe	His	Tyr 150	Glu	Ser	Gln	Asn	Ser 155	Thr	Leu	Pro	Val	Gly 160
30		Leu	Gly	Leu	Thr	Lys 165	Asn	Ile	Leu	Gly	Phe 170	Leu	Phe	Pro	Phe	Leu 175	Ile
		Ile	Leu	Thr	Ser 180	Tyr	Thr	Leu	Ile	Trp 185	Lys	Thr	Leu	Lys	Lys 190	Ala	Tyr
		Glu	Ile	Gln 195	Lys	Asn	Lys	Pro	Arg 200	Lys	Asp	Asp	Ile	Phe 205	Lys	Ile	Ile
35		Ile	Ala 210	Ile	Val	Leu	Phe	Phe 215	Phe	Phe	Ser	Trp	Val 220	Pro	His	Asn	Ile
		Phe 225	Thr	Phe	Met	Val	Leu 230	Ile	Gln	Leu	Gly	Leu 235	Ile	Arg	Asp	Суѕ	Lys 240
40		Ile	Glu	Asp	Ile	Val 245	Asp	Thr	Ala	Met	Pro 250	Ile	Thr	Ile	Cys	Leu 255	Ala
		Tyr	Phe	Gln	Gln 260	Asn	Leu	Asn	Pro	Leu 265	Phe	Tyr	Gly	Phe	Leu 270	Gly	Lys
		Lys	Phe	Lys 275	Lys	Tyr	Phe	Leu	His 280	Ala	Leu	Leu	Lys	Tyr 285	Ile	Pro	Pro
45		Lys	Ala 290	Lys	Ser	His	Ser	Asn 295	Leu	Ser	Thr	Lys	Met 300	Ser	Thr	Leu	Ser

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		Tyr 305	Arg	Pro	Ser	Glu	Gln 310	Gly	Asn	Ser	Ser	Thr 315	Lys	Lys	Pro	Ala	Pro 320
		Cys	Ile	Glu	Val	Glu 325											
5 10	(2)	INFOR	SEQU (A) (B) (C)	JENCE LEI TYI	E CHA NGTH: PE: & RANDI	ARACT 282 amino BDNES	TERIS  ami  aci  ss: s	STICS ino a id sing!	S: acids	5							
		(ii)	MOLI	ECULE	TYI	?E: p	pept:	ide									
		(xi) Ile 1						Met				Pro	Val	Gly	Phe	Val 15	Glu
15		Asn	Gly	Ile	Leu 20	Leu	Trp	Phe	Leu	Cys 25	Phe	Phe	Thr	Val	Tyr 30	Thr	His
		Leu	Ser	Ile 35	Ala	qaA	Ile	Ser	Leu 40	Leu	Phe	Cys	Ile	Phe 45	Ile	Leu	Ser
20		Ile	<b>Asp</b> 50	Tyr	Ala	Leu	qaA	Tyr 55	Glu	Leu	Ser	Ser	Gly 60	His	Tyr	Tyr	Thr
		Ile 65	Val	Thr	Leu	Ser	Val 70	Thr	Phe	Leu	Phe	Gly 75	Tyr	Asn	Thr	Gly	Leu 80
		Tyr	Leu	Leu	Thr	Ala 85	Ile	Ser	Val	Glu	Arg 90	Суѕ	Leu	Ser	Val	Leu 95	Tyr
25		Pro	Ile	Trp	Tyr 100	Arg	Cys	His	Arg	Pro 105	Lys	Tyr	Gln	Ser	Ala 110	Leu	Val
		Сув	Ala	Leu 115	Leu	Trp	Ala	Leu	Ser 120	Cys	Leu	Val	Thr	Thr 125	Мес	Tyr	Val
30		Met	Cys 130	Ile	Asp	Arg	Phe	Glu 135	Glu	Ser	His	Ser	Arg 140	Asn	Asp	Cys	Arg
		Ala 145	Val	Ile	Ile	Phe	Ile 150	Ala	Ile	Leu	Ser	Phe 155	Leu	Val	Phe	Thr	Pro 160
		Ser	Val	Ser	Ser	Thr 165	Ile	Leu	Val	Val	Lys 170	Ile	Arg	Lys	Asn	Thr 175	Trp
35		Ala	Ser	His	Ser 180	Ser	Lys	Leu	Tyr	Ile 185	Val	Ile	Met	Val	Thr 190	Ile	Ile
		Ile	Phe	Leu 195	Ile	Phe	Ala	Met	Pro 200	Met	Arg	Leu	Leu	Tyr 205	Leu	Leu	Tyr
40		Tyr	Glu 210	Tyr	Trp	Ser	Thr	Phe 215	Gly	Asn	Leu	His	His 220	Ile	Ser	Leu	Leu
		Phe 225	Ser	Thr	Ile	Asn	Ser 230	Ser	Ala	Asn	Pro	Phe 235	Ile	Tyr	Phe	Phe	Val 240
		Gly	Ser	Ser	Lys	Lys 245	Lys	Arg	Phe	Lys	Glu 250	Ser	Leu	Lys	Val	Val 255	Leu
45		Thr	Arg	Ala	Phe 260	Lys	Asp	Glu	Met	Gln 265	Pro	Arg	Arg	Gln	Lys 270	Asp	Asn
		Cys	Asn	Thr	Val	Thr	Val	Glu	Thr	Val	Val						

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275 (2) INFORMATION FOR SEQ ID NO:53: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 332 amino acids 5 (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:53: 10 Tyr Asp Phe Leu Arg Val Leu Ile Trp Leu Ile Asn Ile Leu Ala Ile Met Gly Asn Val Met Thr Leu Phe Val Leu Leu Thr Ser Arg Tyr Lys Leu Thr Val Pro Arg Phe Ile Met Asn Leu Ser Phe Ala Asp Phe Cys 15 Met Leu Tyr Leu Leu Ile Ala Ser Val Asp Ser Gln Thr Lys Gly Gln Tyr Tyr Asn His Ala Ile Asp Trp Gln Thr Gly Ser Gly Cys Ser 20 Thr Ala Gly Phe Phe Thr Val Leu Ala Ser Glu Leu Ser Val Tyr Thr Leu Thr Val Ile Thr Leu Glu Arg Trp His Thr Ile Thr Tyr Ala Ile His Ile Asp Gln Lys Leu Arg Leu Arg His Ala Ile Leu Ile Met Leu 25 Gly Gly Trp Leu Phe Ser Ser Leu Ile Ala Met Leu Pro Leu Val Cys Val Ser Asn Tyr Met Lys Val Ser Ile Cys Leu Pro Met Val Glu Thr 30 Thr Leu Ser Gln Val Tyr Ile Leu Thr Ile Leu Ile Leu Asn Val Val Ala Phe Leu Ile Ile Cys Ala Cys Tyr Ile Lys Ile Tyr Phe Ala Val 185 Arg Asn Pro Glu Ile Met Ala Thr Asn Lys Asp Thr Lys Ile Ala Leu 35 Ala Ile Leu Ile Phe Thr Asp Phe Thr Cys Met Pro Ile Ser Phe Phe Ala Ile Ser Ala Ala Phe Lys Val Pro Leu Ile Val Thr Asn Ser Lys 40 Val Leu Leu Val Leu Phe Tyr Pro Ile Asn Ser Cys Ala Asn Pro Phe Leu Tyr Ala Ile Phe Thr Lys Thr Phe Gln Arg Asp Phe Phe Ile Leu Ser Lys Phe Cys Cys Lys Arg Arg Ala Asp Ile Tyr Arg Arg Lys Asp 45

Phe Ser Ala Tyr Thr Ser Asn Cys Lys Lys Gly Phe Thr Gly Ser Asn

300

295

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	Lys 305	Pro	Ser	Gln	Ser	Thr 310	Leu	Lys	Leu	Ser	Thr 315	Leu	His	Суз	Gln	Gly 320
	Thi	Ala	Leu	Leu	Asp 325	Lys	Arg	Arg	Tyr	Thr 330	Glu	Cys				
5		(B (C	UENCI ) LEI ) TYI ) STI	E CHA NGTH: PE: & RANDE	ARACT 336 amino EDNES	TERIS  ami  aci  SS: 8	STICS ino a id sing!	S: acids	5							
10	(ii)	MOT:	) TOI ECULI													
		SEQ						-								
	Tyr 1	Lys	Phe	Leu	Arg 5	Ile	Val	Val	Trp	Phe 10	Val	Ser	Leu	Leu	Ala 15	Leu
15	Let	Gly	Asn	Val 20	Phe	Val	Leu	Leu	Ile 25	Leu	Leu	Thr	Ser	His 30	Tyr	Lys
	Lev	a Asn	Val 35	Pro	Arg	Phe	Ile	Met 40	Asn	Ile	Ala	Phe	Ala 45	Asp	Phe	Cys
20	Met	<b>M</b> et 50	Tyr	Leu	Leu	Leu	Ile 55	Ala	Ser	Val	Asp	Leu 60	Tyr	Thr	His	Ser
	Gl: 65	Tyr	Tyr	Asn	His	Ala 70	Ile	Asp	Trp	Gln	Thr 75	Gly	Pro	Gly	Cys	Asn 80
	Thi	Ala	Gly	Phe	Phe 85	Thr	Val	Phe	Ala	Ser 90	Glu	Leu	Ser	Val	Tyr 95	Thr
25	Let	1 Thr	Val	Ile 100	Thr	Leu	Glu	Arg	Trp 105	Tyr	Ala	Ile	Thr	Phe 110	Ala	Met
	Arg	g Leu	<b>Asp</b> 115	Arg	Lys	Ile	Arg	Leu 120	Arg	His	Ala	Cys	Ala 125	Ile	Met	Val
30	Gly	7 Gly 130	Trp	Val	Сув	Cys	Phe 135	Leu	Leu	Ala	Leu	Leu 140	Pro	Leu	Val	Gly
	Ile 145	e Ser	Ser	Tyr	Ala	Lys 150	Val	Ser	Ile	Cys	Leu 155	Pro	Met	Thr	Glu	Thr 160
	Pro	) Leu	Ala	Leu	Ala 155	Tyr	Ile	Val	Phe	Val 170	Leu	Thr	Leu	Asn	Ile 175	Val
35	Ala	a Phe	Val	Ile 180	Val	Cys	Сув	Сув	Tyr 185	Val	Lys	Ile	Tyr	Ile 190	Thr	Val
	Arg	g Asn	Pro 195	Gln	Tyr	Asn	Pro	Gly 200	Asp	Lys	Asp	Thr	Lys 205	Ile	Ala	Lys
40	Arg	<b>Me</b> t 210		Val	Leu	Ile	Phe 215	Thr	Asp	Phe	Ile	Cys 220	Met	Ala	Pro	Ile
	Se: 22!	r Phe	Tyr	Ala	Leu	Ser 230		Ile	Leu	Asn	Lys 235	Pro	Leu	Ile	Thr	Val 240
	Se:	r Asn	Ser	Lys	Ile 245	Leu	Leu	Val	Leu	Phe 250	Tyr	Pro	Leu	Asn	Ser 255	Cys
45	Ala	a Asn	Pro	Phe 260	Leu	Tyr	Ala	Ile	Phe 265	Thr	Lys	Ala	Phe	Gln 270	Arg	Asp

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	Val	Phe	Ile 275	Leu	Leu	Ser	Lys	Phe 280	Gly	Ile	Cys	Lys	Arg 285	Gln	Ala	Gln
	Ala	Tyr 290	Arg	Gly	Gln	Arg	Val 295	Pro	Pro	Lys	Asn	Ser 300	Thr	Asp	Ile	Gln
5	Val 305	Gln	Lys	Val	Thr	His 310	qaA	Met	Arg	Gln	Gly 315	Ala	Leu	Asn	Met	Glu 320
	Asp	Val	Val	Glu	Leu 325	Ile	Glu	Asn	Ser	His 330	Leu	Thr	Pro	Lys	Lys 335	Gln
10	(2) INFO	SEQUAL (A)		E CHA NGTH PE: & RANDI	ARACT 32 mino DNES	TERIS 7 am: 5 ac: 5S: 8	STICS ino a id singl	S: acids	5							
15	(ii)	WOT														
		SEQ! Asn									Ile	Ser	Ile	Leu	Ala 15	Ile
20	Thr	Gly	Asn	Ile 20	Ile	Val	Leu	Val	Ile 25	Leu	Thr	Thr	Ser	Gln 30	Tyr	Lys
	Leu	Thr	Val 35	Pro	Arg	Phe	Leu	<b>M</b> et <b>4</b> 0	Asn	Ile	Ala	Phe	Ala 45	qaA	Leu	Cys
	Ile	Gly 50	Ile	Tyr	Leu	Leu	Leu 55	Ile	Ala	Ser	Val	Asp 60	Ile	His	Thr	Lys
25	Ser 65	Gln	Tyr	His	Asn	Tyr 70	Ala	Ile	Asp	Trp	Gln 75	Arg	Gly	Ala	Gly	Cys 80
	qaA	Ala	Ala	Gly	Phe 85	Phe	Thr	Val	Phe	Ala 90	Ser	Glu	Leu	Ser	<b>Va</b> l 95	Tyr
30	Thr	Leu	Thr	Ala 100	Ile	Thr	Leu	Glu	Arg 105	Trp	His	Thr	Ile	Thr 110	His	Ile
	Met	Gln	Ile 115	qaA	Сув	Lys	Val	Gln 120	Leu	Arg	His	Ala	Ala 125	Ser	Val	Met
	Val	<b>Met</b> 130	Gly	Trp	Ile	Phe	<b>Ala</b> 135	Phe	Ala	Ala	Ala	Leu 140	Phe	Pro	Ile	Phe
35	Gly 1 <b>4</b> 5	Ile	Ser	Ser	Tyr	<b>M</b> et 150	Lys	Val	Ser	Ile	Cys 155	Leu	Pro	Leu	Ile	Asp 160
	Ser	Pro	Leu	Ser	Gln 165	Leu	Tyr	Val	Met	Ser 170	Leu	Leu	Val	Leu	<b>As</b> n 175	Val
40	Leu	Ala	Phe	Val 180	Val	Ile	Cys	Gly	Сув 185	Tyr	Thr	His	Ile	Tyr 19∪	Leu	Thr
	Val	Arg	Asn 195	Pro	Asn	Ile	Val	Ser 200	Ser	Ser	Ser	qaA	Thr 205	Arg	Ile	Ala
	Lys	Arg 210	Met	Leu	Ile	Phe	Thr 215	qaA	Phe	Leu	Leu	Pro 220	Ile	Ser	Phe	Phe
45	Ala 225	Ile	Ser	Ala	Ser	Leu 230	Lys	Val	Pro	Leu	Ile 235	Thr	Val	Ser	Lys	Ala 240
	Lys	Ile	Leu	Leu	Val	Leu	Phe	His	Pro	Ile	Asn	Ser	Cys	Ala	naA	Pro

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						245					250					255	
		Phe	Leu	Tyr	Ala 260	Ile	Phe	Thr	Lys	<b>As</b> n 265	Phe	Arg	Arg	Asp	Phe 270	Phe	Ile
5		Leu	Leu	<b>Ser</b> 275	Lys	Cys	Gly	Cys	Tyr 280	Glu	Met	Gln	Ala	Gln 285	Ile	Tyr	Arg
		Thr	Glu 290	Thr	Ser	Ser	Thr	Val 295	His	Asn	Thr	His	Pro 300	Arg	Asn	Gly	His
		Cys 305	Ser	Ser	Ala	Pro	<b>Arg</b> 310	Val	Thr	Ser	Gly	Ser 315	Ser	Arg	Tyr	Ile	Leu 320
10		Val	Pro	Leu	Ser	Leu 325	Gln	Asn									
15	(2)		SEQU (A) (B) (C) (D)	JENCI LEI TYI STI TOI	CHI NGTH PE: & RANDI POLOC	ARACT : 309 emino SDNES SY:	reris am: ac: SS: s linea	STICS ino a id singl	S: acida	5							
20		(xi) Ser 1	SEQU Met	JENCI Leu	E DES Ala	SCRII Ala 5	Tyr Tyr	N: SI Met	EQ II Phe	NO Leu	:56: Leu 10	Ile	Val	Leu	Gly	Phe 15	Pro
		Ile	Asn	Phe	Leu 20	Thr	Leu	Tyr	Val	Thr 25	Val	Gln	His	Lys	Lys 30	Leu	Arg
25		Thr	Pro	Ile 35	Asn	Tyr	Ile	Leu	Leu 40	Asn	Leu	Ala	Val	Ala 45	Asp	Leu	Phe
		Met	Val 50	Leu	Gly	Gly	Phe	Thr 55	Ser	Thr	Leu	Tyr	Thr 60	Ser	Leu	His	Gly
		Tyr 65	Phe	Val	Phe	Gly	Pro 70	Thr	Gly	Сув	Asn	Leu 75	Glu	Gly	Phe	Phe	Ala 80
30		Thr	Leu	Gly	Gly	Clu 85	Ile	Ala	Leu	Trp	Ser 90	Leu	Trp	Leu	Ala	Ile 95	Glu
		Arg	Tyr	Val	Val 100		Сув	Lys	Pro	Met 105		Asn	Phe	Arg	Phe 110	Gly	Glu
35		Asn		Ala 115										<b>M</b> et 125		Leu	Ala
		Сув	Ala 130		Pro	Pro	Ile	Ala 135		Trp	Ser	Arg	Tyr 140		Pro	Glu	Gly
		Leu 145		аұЭ	Ser	Cys	Gly 150		Asp	Tyr	Tyr	Thr 155		Lys	Pro	Glu	Val 160
40		Asn	Asn	Glu	Ser	Phe 165		Ile	Tyr	Met	Phe 170		Val	His	Phe	Thr 175	Ile
		Pro	Leu	Ile	Ile 180		Phe	Cys	Tyr	Gly 185		Leu	Val	Phe	Thr 190		Lys
45		Glu	Ala	Ala 195		Gln	Gln	Gln	Glu 200		Ala	Thr	Thr	Gln 205	Lys	Ala	Glu
		Lys	Glu 210		Thr	Arg	Met	Val 215		lle	Met	. Val	11e		Pho	Leu	Ile

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	Cy:	Trp	Val	Pro	Tyr	Ala 230	Ser	Val	Ala	Phe	Tyr 235	Ile	Phe	Thr	His	Gln 240
	Gl	/ Ser	Asn	Phe	Gly 245	Pro	Ile	Phe	Met	Arg 250	Ile	Pro	Ala	Phe	Phe 255	Ala
5	Ly:	Ser	Ala	Ala 260	Ile	Tyr	Asn	Pro	Val 265	Ile	Tyr	Ile	Ile	Phe 270	Asn	Lys
	Glı	n Phe	Arg 275	Asn	Суѕ	Met	Leu	Gln 280	Leu	Ile	Cys	Cys	Gly 285	Lys	Asn	Pro
10	Lev	Gly 290	-	Asp	Glu	Ala	Ser 295	Ala	Thr	Val	Ser	Lys 300	Arg	Glu	Thr	Ser
	Gl: 305	val	Ala	Pro	Ala											
15	(i)	(B (C	UENC: ) LE: ) TY: ) ST: ) TO:	E CHA NGTH PE: 8 RANDI POLO	ARAC : 29 emino EDNES GY:	reris 7 am: 5 ac: SS: s linea	STICS ino a id sing: ar	S: acids	5							
20	(xi)	SEQ : Ile	UENC	E DES	SCRI	PTIO	N: S1	_			Thr	Asn	Gly	Leu	Val 15	Leu
	Ala	Ala	Thr	Met 20	Lys	Phe	Lys	Lys	Leu 25	Pro	His	Pro	Ile	Asn 30	Trp	Ile
25	Lev	ı Val	Asn 35	Leu	Ala	Val	Ala	Asp 40	Ile	Ala	Gly	Thr	Val 45	Ile	Ala	Ser
	Thi	Ile 50	Ser	Val	Val	Asn	Gln 55	Val	тут	Gly	Tyr	Phe 60	Val	Leu	Gly	His
30	Pro 65	Met	Сув	Val	Leu	Glu 70	Gly	Tyr	Thr	Val	Ser 75	Leu	Cys	Gly	Ile	Thr 80
	Gly	z Leu	Trp	Ser	Leu 85	Ala	Ile	Ile	Ser	Trp 90	Glu	Arg	Trp	Met	Val 95	Val
	Суя	Lys	Pro	Phe 100	Gly	Asn	Val	Arg	Phe 105	Asp	Ala	Lys	Ile	Ala 110	Ile	Val
35	Gly	, Ile	Ala 115	Phe	Ser	Trp	Ile	Trp 120	Ala	Ala	Val	Trp	Thr 125	Ala	Pro	Pro
	Ile	Phe 130	-	Trp	Ser	Arg	Tyr 135	Trp	Pro	His	Gly	Leu 140	Lys	Thr	Ser	Cys
40	Gl <sub>3</sub> 145	Pro	Asp	Val	Phe	Ser 150	Gly	Ser	Ser	Tyr	Pro 155	Gly	Val	Gln	Ser	Leu 160
	Lei	Cys	Ile	Thr	Pro 165	Leu	Ser	Ile	Ile	Val 170	Leu	Cys	Tyr	Leu	Gln 175	Val
	Tr	Thr	Ala	Ile 180	Arg	Ala	Val	Ala	Lys 185	Gln	Gln	Lys	Glu	Ser 190	Glu	Ser
45	Thi	Gln	Lys 195	Ala	Glu	Lys	Glu	Val 200	Thr	Arg	Met	Trp	<b>Val</b> 205	Met	Val	Leu
	Ala	Phe	Cys	Phe	Cys	Trp	Gly	Pro	Tyr	Ala	Phe	Phe	Ala	Cys	Phe	Ala

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			210					215					220				
		Ala 225	Ala	Asn	Pro	Gly	Tyr 230	Pro	Phe	His	Pro	Leu 235	Met	Ala	Ala	Leu	Pro 240
5		Ala	Phe	Phe	Ala	Lys 245	Ser	Ala	Thr	Ile	Tyr 250	Asn	Pro	Val	Ile	Tyr 255	Val
		Phe	Met	Asn	Arg 260	Gln	Phe	Arg	Asn	Сув 265	Ile	Leu	Gln	Leu	Phe 270	Gly	Lys
		Lys	Val	Asp 275	qaA	Gly	Ser	Glu	Leu 280	Ser	Ser	Ala	Ser	Lys 285	Thr	Glu	Val
10		Ser	Ser 290	Val	Ser	Ser	Val	Ser 295	Pro	Ala							
15	(2)	INFOR	SEQU (A) (B) (C) (D)	JENCE LEI TYI STI TOI	E CHANGTH: PE: 6 RANDI	ARACT 297 mind EDNES SY:	reris 7 ami 5 aci 88: s linea	STICS ino a id sing]	S: acids	3							
20		(xi) Arg 1	SEQ0 Cys	JENCI Phe	Val	SCRII Val 5	Thr	N: SI Ala	SQ II Ser	NO Val	:58: Phe 10	Thr	Asn	Gly	Leu	Val 15	Leu
		Ala	Ala	Thr	Met 20	Lys	Phe	Lys	Lys	Leu 25	Arg	His	Pro	Leu	Asn 30	Trp	Ile
25		Leu	Val	Asn 35	Ile	Ala	Val	Ala	Asp 40	Ile	Ala	Gly	Thr	Val 45	Ile	Ala	Ser
		Thr	Ile 50	Ser	Ile	Val	Asn	Gln 55	Val	Ser	Gly	Tyr	Phe 60	Val	Leu	Gly	His
		Pro 65	Met	Cys	Val	Leu	Glu 70	Gly	Tyr	Thr	Val	Ser 75	Leu	Cys	Gly	Ile	Thr 80
30		Gly	Leu	Trp	Ser	Leu 85	Ala	Ile	Ile	Ser	Trp 90	Glu	Arg	Trp	Leu	Trp 95	Cys
		Lys	Pro	Phe	Gly 100	Asn	Val	Arg	Phe	Asp 105		Lys	Ile	Ala	Ile 110	Val	Gly
35		Ile	Ala	Phe 115		Trp	Ile	Trp			Val	Trp	Thr	Ala 125	Pro	Pro	Ile
		Phe	Gly 130		Ser	Arg	Tyr	Trp 135		His	Gly	Leu	Lys 140	Thr	Ser	Сув	Gly
		Pro 145		Val	Phe	Ser	Gly 150		Ser	Туг	Pro	Gly 155	Val	Gln	Ser	Leu	Val 160
40		Ile	Met	Val	Thr	Cys 165	Cys	Ile	Ile	Pro	Ile 170		Ile	Ile	Leu	Cys 175	Tyr
		Leu	Gln	Val	Trp 180		Ala	Ile	Arg	Ala 185		Ala	Lys	Gln	Gln 190		Glu
45		Ser	Glu	Ser 195		Gln	Lys	Ala	Glu 200		Glu	Val	Thr	Arg 205		Leu	Phe
		Ala	Tyr 210		Val	Cys	Trp	Gly 215		Tyr	Thr	Phe	Phe 220		Суѕ	Phe	Ala

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	Ala 225	a Ala	Asn	Pro	Gly	Tyr 230	Ala	Phe	His	Pro	Leu 235	Met	Ala	Ala	Leu	Pro 240
	Ala	а Туг	Phe	Ala	Lys 245	Ser	Ala	Thr	Ile	Tyr 250	Asn	Pro	Val	Ile	Tyr 255	Val
5	Phe	Met	Asn	Arg 260	Gln	Phe	Arg	Asn	Cys 265	Ile	Leu	Gln	Leu	Phe 270	Gly	Lys
	Lys	Val	Asp 275	qaA	Gly	Ser	Glu	Leu 280	Ser	Ser	Ala	Ser	Lys 285	Thr	Glu	Val
10	Sea	Ser 290		Ser	Ser	Val	Ser 295	Pro	Ala							
15		(B (C	UENCI ) LEI ) TYI ) STI	E CHI NGTH PE: 8 RANDI	ARACT : 305 amino BDNES	TERIS  auni  aci  ss: s	STICS ino a id sing:	S: acids	5							
	(ii)	MOL.	) TO: ECUL													
20		SEQ Ala						_			Ile	Gly	Phe	Pro	Leu 15	Leu
	Va]	. Ala	Thr	Leu 20	Ala	Туг	Lys	Lys	Leu 25	Arg	Gln	Pro	Asn	Tyr 30	Ile	Leu
	Va]	Asn	Val 35	Ser	Phe	Gly	Gly	Phe 40	Leu	Leu	Сув	Ile	Phe 45	Ser	Val	Phe
25	Pro	Val 50	Phe	Val	Ala	Ser	Сув 55	Asn	Gly	Tyr	Phe	Val 60	Phe	Gly	Arg	His
	Va] 65	. Сув	Ala	Leu	Glu	Gly 70	Phe	Leu	Gly	Thr	Val 75	Ala	Gly	Leu	Val	Thr 80
30	Gl <sub>3</sub>	Trp	Ser	Leu	Ala 85	Phe	Leu	Ala	Phe	Glu 90	Arg	Tyr	Ile	Val	Ile 95	Сув
	Lys	Pro	Phe	Gly 100	Asn	Phe	Arg	Phe	Ser 105	Ser	Lys	His	Ala	Leu 110	Thr	Val
	Va]	Ile	Ala 115	Thr	Trp	Thr	Ile	Gly 120	Ile	Gly	Val	Ser	Ile 125	Pro	Pro	Phe
35	Phe	Gly 130	-	Ser	Arg	Phe	Ile 135	Pro	Glu	Gly	Leu	Gln 140	Сув	Ser	Сув	Gly
	Pro 145	Asp	Lys	Tyr	Thr	Val 150	Gly	Thr	Lys	Tyr	Arg 155	Ser	Glu	Ser	Tyr	Thr 160
40	Trī	Phe	Leu	Phe	Ile 165	Phe	Cys	Phe	Ile	Val 170	Pro	Leu	Ser	Leu	Ile 175	Cys
	Phe	Ser	Tyr	Thr 180	Gln	Leu	Leu	Arg	Ala 185	Leu	Lys	Ala	Val	Ala 190	Ala	Gln
	Glr	Gln	Glu 195	Ser	Ala	Thr	Thr	Gln 200	Lys	Ala	Glu	Arg	Glu 205	Val	Ser	Arg
45	Met	Val 210		Val	Met	Val	Gly 215	Ser	Phe	Cys	Val	Cys 220	Tyr	Val	Pro	Tyr
	Ala	Ala	Phe	Ala	Met	Tyr	Met	Val	Asn	Asn	Arg	Asn	His	Gly	Leu	Asp

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		225					230					235					240
		Leu	Arg	Leu	Val	Arg 245	Ile	Pro	Ser	Phe	Phe 250	Ser	Lys	Ser	Ala	Cys 255	Ile
5		Tyr	Asn	Pro	Ile 260	Ile	Tyr	Сув	Phe	Met 265	naA	Lys	Gln	Phe	Gln 270	Ala	Сув
		Ile	Met	Met 275	Val	Cys	Gly	Lys	Ala 280	Met	Met	Glu	Ser	Asp 285	Thr	Cys	Ser
		Ser	Gln 290	Lys	Thr	Glu	Val	Ser 295	Thr	Val	Ser	Ser	Thr 300	Gln	Val	Gly	Pro
10		Asn 305															
15	(2)	INFOR	SEQU (A) (B) (C) (D)	JENCE LEN TYP STP TOP	CHARGETH: PE: 8  RANDE POLOG	RACT 293 mino DNES SY: ]	TERIS  ami aci SS: s  lines	STICS ino a id singl	3: acida	3							
20		(xi) Leu 1										Leu	Val	Thr	Val	Ile 15	Gly
		Asn	Ile	Ser	Ile 20	Ile	Val	Ala	Ile	Ile 25	Ser	Asp	Pro	Cys	Leu 30	His	Thr
25		Pro	Met	Tyr 35	Phe	Phe	Leu	Ser	Asn 40	Leu	Ser	Phe	Val	Asp 45	Ile	Cys	Phe
		Ile	Ser 50	Thr	Thr	Val	Pro	Val 55	Asn	Thr	Gln	Thr	Gln 60	Asn	Asn	Val	Ile
		Thr 65	Тут	Ala	Gly	Сув	Ile 70	Thr	Gln	Ile	Tyr	Phe 75	Phe	Leu	Leu	Phe	Val 80
30		Glu	Leu	qaA	Asn	Phe 85	Leu	Leu	Thr	Ile	<b>M</b> et 90	Ala	Tyr	qaA	Arg	Tyr 95	Val
		Ala	Ile	Сув	His 100	Pro	Met	His	Tyr	Thr 105	Val	Ile	Met	naA	Tyr 110	Lys	Leu
35		Сув	Gly	Phe 115	Leu	Val	Leu	Val	Ser 120	Trp	Ile	Val	Ser	Val 125	Leu	His	Ala
		Leu	Phe 130	Gln	Ser	Leu	Ala	Leu 135	Pro	Phe	Сув	Thr	His 140	Leu	Glu	Ile	Pro
		His 145		Phe	Cys	Glu	Pro 150	Asn	Gln	Val	Ile	Gln 155	Leu	Thr	Cys	Ser	Asp 160
40		Ala	Phe	Leu	Asn	Asp 165	Leu	Val	Ile	Tyr	Phe 170	Thr	Leu	Val	Leu	Leu 175	Ala
		Thr	Val	Pro	Ile 180	Ala	Gly	Ile	Phe	Tyr 185		Tyr	Phe	Ala	Ile 19:	Ser	Ser
45		Val	His	Gly 195	Lys	Tyr	Lys	Ala	Phe 200		Thr	Cys	Ala	Ser 205		Leu	Ser
		Val	Val 210		Leu	Phe	Tyr	Cys 215		Gly	Leu	Gly	Val 220		Leu	Ser	Ser

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	Ala 225	Ala	Asn	Asn	Ser	Leu 230	Ser	Ala	Thr	Ala	Ser 235	Val	Met	Tyr	Thr	Val 240
		Thr	Pro	Met	Val 245		Pro	Phe	Ile	Tyr 250	Ser	Leu	Arg	Asn	Lys 255	Asp
5	Val	Lys	Ser	Val 260	Leu	Lys	Lys	Thr	Leu 265	Cys	Glu	Glu	Val	Ile 270	Arg	Ser
	Pro	Pro	Ser 275	Leu	Leu	His	Phe	Phe 280	Leu	Val	Leu	Cys	His 285	Leu	Pro	Cys
10	Phe	Ile 290	Phe	Сув	Tyr											
	(2) INFOR	SEQU		CHA	ARAC	TERIS	STICS	3:								
15	(ii)	(B) (C) (D)	TYI STI TOI	PE: &  CANDI  POLOC	amino EDNES GY:	o aci SS: s linea	id sing: ar		•							
20	(xi) Leu 1	SEQI Leu									Leu	Ala	Thr	Val	Leu 15	Gly
	Asn	Leu	Leu	Ile 20	Ile	Leu	Ala	Ile	Gly 25	Gly	qaA	Ser	Arg	Leu 30	His	Thr
	Pro	Met	Tyr 35	Phe	Phe	Leu	Ser	Asn 40	Leu	Ser	Phe	Val	Asp 45	Val	сув	Phe
25	Ser	Ser 50	Thr	Thr	Val	Pro	Lys 55	Val	Leu	Ala	Asn	His 60	Ile	Leu	Gly	Ser
	Gln 65	Ala	Ile	Ser	Phe	Ser 70	Gly	Cys	Leu	Thr	Gln 75	Leu	Tyr	Phe	Leu	Ala 80
30	Val	Phe	Gly	Asn	Met 85	Asp	Asn	Phe	Leu	Leu 90	Ala	Val	Met	Ser	Tyr 95	Asp
	Arg	Туr	Val	Ala 100	Ile	Суз	His	Pro	Leu 105	His	Tyr	Thr	Thr	Ile 110	Arg	Gln
	Leu	Cys	<b>Va</b> l 115	Leu	Leu	Val	Val	Gly 120	Ser	Trp	Val	Val	Ala 125	Asn	Met	Asn
35	Cys	Leu 130	Leu	His	Ile	Leu	Ile 135	Met	Ala	Arg	Lys	Ser 140	Phe	Сув	Ala	Asp
	Leu 145	Pro	His	Phe	Phe	Cys 150	Asp	Gly	Thr	Pro	Leu 155	Leu	Lys	Leu	Ser	Суs 160
40	Ser	Asp	Thr	His	Leu 165	Asn	Glu	Leu	Met	Ile 170	Leu	Thr	Glu	Gly	Ala 175	Val
	Val	Met	Val	Thr 180	Pro	Phe	Val	Сув	Ile 185	Leu	Ile	Ser	Tyr	Ile 190	His	Ile
	Thr	Cys	Ala 195	Val	Leu	Arg	Val	Ser 200	Ser	Pro	Arg	Gly	Gly 205	Trp	Lys	Ser
45	Phe	Ser 210	Thr	Cys	Cly	Ser	His 215	Ile	Ala	Val	Val	Cys 220	Leu	Phe	Tyr	Gly
	Thr	Val	Ile	Ala	Val	Tyr	Phe	Asn	Pro	Ser	Ser	Ser	His	Leu	Ala	Gly

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		225					230					235					240
		Arg	Ąsp	Met	Ala	Ala 245	Ala	Val	Met	Tyr	Ala 250	Val	Val	Thr	Pro	<b>Met</b> 255	Ile
5		Asn	Pro	Phe	Ile 260	Tyr	Ser	Leu	Arg	Asn 265	Ser	Asp	Met	Lys	Ala 270	Ala	Leu
		Arg	Lys	Val 275	Leu	Ala	Met	Arg	Phe 280	Pro	Ser	Lys	Gln				
10	(2)		SEQU (A) (B) (C) (D)	JENCE LEN TYE STE TOE	CHA IGTH: E: a ZANDE POLOG	RACT 277 mino DNES Y: 1	ERIS ami aci S: s inea	TICS no a d ingl	: cids	3							
15		(xi)							Q II	OM C	62:						
		Leu 1	Leu	Phe	Leu	Leu 5	Phe	Leu	Val	Met	Tyr 10	Leu	Leu	Thr	Val	Val 15	Gly
		Asn	Leu	Ala	Ile 20	Ile	Ser	Leu	Val	Gly 25	Ala	His	Arg	Сув	Leu 30	Gln	Pro
20		His	Thr	Pro 35	Met	Tyr	Phe	Phe	Leu 40	Cys	Asn	Leu	Ser	Phe 45	Leu	Glu	Ile
		Trp	Phe 50	Thr	Thr	Ala	Cys	Val 55	Pro	Lys	Thr	Leu	Ala 60	Thr	Phe	Ala	Pro
25		Arg 65	Gly	Gly	Val	Ile	Ser 70	Leu	Ala	Gly	Cys	Ala 75	Thr	Lys	Tyr	Phe	Val 80
					Gly	85					90					95	
					Leu 100					105					110		
30		_		115	Ile				120					125			
			130		Ile			135					140				
35		145					150					155					Trp 160
					Ser	165					170					175	
	•				Phe 180					185					190		
40				195					200					205			Ser
			210					215					220				Thr
45		225					230					235					Thr 240
		Lys	Ala	Ile	Thr	Val	Leu	Asn	Thr	Ile	Val	Thr	Pro	Val	Leu	Asn	Pro

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245 250 Phe Ile Tyr Thr Leu Arg Asn Lys Asp Val Lys Glu Ala Leu Arg Arg Thr Val Lys Gly Lys 5 275 (2) INFORMATION FOR SEQ ID NO:63: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 273 amino acids (B) TYPE: amino acid(C) STRANDEDNESS: single 10 (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:63: Leu Ile Phe Ala Leu Phe Leu Ser Met Tyr Leu Val Thr Val Leu Gly 15 Asn Leu Leu Ile Ile Met Ala Ile Ile Thr Gln Ser His Leu His Thr Pro Met Tyr Phe Phe Leu Ser Phe Val Asp Ile Cys Phe Thr Ser Thr Thr Ile Pro Leu Val Asn Ile Tyr Thr Gln Ser Lys Ser Ile Thr Tyr 20 Glu Asp Cys Ile Ser Leu Val Phe Ala Glu Leu Gly Asn Phe Leu Leu 65 70 75 80 Ala Val Met Ala Tyr Asp Arg Tyr Val Ala Xaa Cys His Pro Leu Cys 25 Tyr Thr Val Ile Val Asn His Arg Leu Cys Ile Leu Leu Leu Leu Leu Ser Trp Val Ile Ser Ile Phe Arg Ala Phe Ile Gln Ser Leu Ile Val 30 Leu Gln Leu Thr Phe Cys Gly Asp Val Lys Ile Pro His Phe Phe Cys Glu Leu Asn Gln Leu Ser Gln Leu Thr Cys Ser Asp Asn Phe Pro Ser 155 His Leu Ile Met Asn Leu Val Pro Val Met Leu Ala Ala Ile Ser Phe 35 Ser Gly Ile Leu Tyr Ser Tyr Phe Ser Ile Ser Thr Val Gln Gly Lys 185 Tyr Lys Ala Phe Ser Thr Cys Ala Ser His Leu Ser Ile Val Ser Leu 200 40 Phe Tyr Ser Thr Gly Leu Gly Val Tyr Val Ser Ser Ala Val Val Gln Ser Ser His Ser Ala Ala Ser Ala Ser Val Met Tyr Thr Val Val Pro 235 Met Leu Asn Pro Phe Ile Tyr Ser Leu Arg Asn Lys Asp Val Lys Arg 45 Ala Leu Glu Arg Leu Leu Glu Gly Asn Cys Lys Val His His Trp Thr - 119 -

Gly

5	(2)	INFOR (i)	SEQU (A) (B) (C) (D)	ENCE LEN TYP STR TOP	CHA GTH: E: a ANDE OLOG	RACT 269 mino DNES Y: 1	ERIS ami aci S: s inea	TICS no a d ingl	: cids	i							
10		(xi) Leu 1	SEQU Phe	ENCE Tyr	DES Ala	CRIP Leu 5	TION Phe	: SE Leu	Q II Val	NO: Met	64: Tyr 10	Leu	Thr	Thr	Ile	Leu 15	Gly
		Asn	Leu	Leu	Ile 20	Ile	Val	Leu	Val	Gln 25	Leu	qaA	Ser	Gln	Leu 30	His	Thr
15		Pro	Met	Tyr 35	Leu	Phe	Leu	Ser	Asn 40	Leu	Ser	Phe	Ser	<b>Asp</b> 45	Leיı	Cys	Phe
		Ser	Ser 50	Leu	Lys	Leu	Leu	Gln 55	Asn	Met	Arg	Ser	Gln 60	Asp	Thr	Ser	Ile
20		Pro 65	Tyr	Gly	Gly	Сув	Leu 70	Ala	Gln	Thr	Tyr	Phe 75	Phe	Met	Val	Phe	Gly 80
		qaA	Leu	Ser	Phe	Leu 85	Leu	Val	Ala	Met	Ala 90	Tyr	Asp	Arg	Tyr	Val 95	Ala
		Ile	Сув	Phe	Leu 100	Pro	His	Tyr	Thr	Ser 105	Ile	Met	Ser	Pro	<b>Lys</b> 110	Leu	Cys
25		Thr	Сув	Leu 115	Val	Leu	Leu	Leu	Trp 120	Met	Leu	Thr	Thr	Ser 125	His	Met	Met
		Thr	Leu 130	Leu	Ala	Ala	Arg	Leu 135	Ser	Phe	Cys	Glu	Asn 140	Asn	Try	Leu	Asn
30		Phe 145	Phe	Сув	Ąsp	Leu	Phe 150	Val	Leu	Leu	Lys	Ile 155	Ala	Cys	Ser	Asp	Thr 160
		Tyr	Ile	Asn	Glu	Leu 165	Phe	Ile	Met	Ser	Thr 170	Leu	Leu	Ile	Ile	Ile 175	Pro
		Phe	Phe	Leu	Ile 180	Val	Met	Ser	Tyr	Ala 185		Val	Pro	Ser	Thr 190	Gln	Gly
35		Ile	Сув	Lys 195	Val	Phe	Ser	Thr	Сув 200	Gly	Ser	His	Leu	Ser 205	Val	Val	Ser
		Leu	Phe 210	Tyr	Gly	Thr	Ile	Ile 215		Leu	Tyr		Cys 220		Ala	Gly	Asn
40		Asn 225	Ser	Thr	Val	Lys	Glu 230	Met	Val	Met	Ala	Met 235	Met	Tyr	Thr	Val	Val 240
		Thr	Pro	Met	Ile	Asn 245		Phe	Ile	Tyr	Ser 250		Arg	Asn	Arg	<b>Asp</b> 255	Leu
		Arg	Ala	Leu	11e 260	Arg	Val	Ile	Cys	Ser 265		Ile	Thr	Leu			

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	(ii)	(D)	TOI CULI	POLO	3Y: 3	linea	ar	re								
5	1	Leu	Phe	Phe	Leu 5	Ser	Leu	Leu	Xaa	Tyr 10					15	
			Leu	20					25					30		-
10	Pro	Met	Tyr 35	Phe	Phe	Leu	Phe	Leu 40	Glu	Ile	Trp	Tyr	Val 45	Thr	Val	Thr
	Ile	Pro 50	Lys	Leu	Met	Gly	Phe 55	Ile	Gly	Ser	Lys	Glu 60	Asn	His	Gly	Gln
	Leu 65	Ile	Ser	Phe	Phe	<b>Ala</b> 70	Сув	Met	Thr	Gln	Leu 75	Tyr	Phe	Phe	Leu	Gly 80
15	Leu	Gly	Сув	Thr	Glu 85	Cys	Val	Leu	Leu	Ala 90	۷al	Met	Ala	Туг	<b>As</b> p 95	Arg
	Tyr	Val	Ala	Ile 100	аұЭ	His	Pro	Leu	His 105	Tyr	Pro	Val	Ile	Val 110	Ser	Ser
20	Arg	Ile	Glx 115	Val	Leu	Gly	Ser	Trp 120	Ala	Gly	Gly	Phe	Gly 125	Ile	Ser	Met
	Val	Lys 130	Val	Phe	Leu	Ile	Ser 135	Arg	Leu	Ser	Tyr	Cys 140	Gly	Pro	Asn	Thr
	Ile 145	Asn	His	Phe	Phe	Cys 150	qaA	Val	Ser	Pro	Leu 155	Leu	Asn	Leu	Ser	Cys 160
25	Thr	qaA	Met	Ser	Thr 165	Ala	Glu	Leu	Thr	<b>Asp</b> 170	Phe	Val	Ile	Ala	Ile 175	Phe
	Ile	Leu	Leu	Gly 180	Pro	Leu	Ser	Val	Thr 185	Gly	Ala	Ser	Tyr	Met 190	Arg	Ile
30	Pro	Ser	<b>Ala</b> 195	Ala	Gly	Arg	His	Lys 200	Ala	Phe	Ser	Thr	Сув 205	Ala	Ser	His
	Leu	Thr 210	Val	Val	Ile	Ile	Phe 215	Tyr	Ala	Ala	Ser	Ile 220	Phe	Ile	Tyr	Ala
	Arg 225	Pro	Lys	Ala	Leu	Ser 230	Ala	Phe	Thr	qaA	Asn 235	Lys	Leu	Va.i.	Ser	Val 240
35	Leu	Tyr	Ala	Val	ile 245	Val	Pro	Leu	Phe	<b>Asn</b> 250	Pro	Ile	Ile	Tyr	Cys 255	Leu
	Arg	Asn	Gln	<b>Asp</b> 260	Val	Lys	Arg	Ala	<b>Leu</b> 265	Arg	Arg	Thr	Leu	His 270	Leu	Ala
10	Gln	Asp	Gln 275	Glu	Ala	Asn	Thr	Asn 280	Lys	Gly	Ser	Lys	Ile 285	Gly		

## (2) INFORMATION FOR SEQ ID NO:66: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 275 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single

45

- (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide

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		(xi) Leu 1		JENCE Phe								Leu	Thr	Thr	Phe	Leu 15	Gly
5		Asn	Leu	Leu	Ile 20	Val	Val	Leu	Val	Gln 25	Leu	Asp	Ser	His	Leu 30	His	Thr
		Pro	Met	Tyr 35	Leu	Phe	Leu	Ser	Asn 40	Leu	Ser	Phe	Ser	Asp 45	Leu	Cys	Phe
		Ser	Ser 50	Val	Thr	Met	Leu	Lys 55	Leu	Leu	Gln	Asn	Ile 60	Gln	Ser	Gln	Val
10		Pro 65	Ser	Ile	Ser	Tyr	Ala 70	Gly	Сув	Leu	Trp	Ile 75	Phe	Phe	Phe	Leu	Leu 80
		Phe	Gly	Tyr	Leu	Gly 85	Asn	Phe	Leu	Leu	Val 90	Ala	Met	Ala	Tyr	<b>Asp</b> 28	Arg
15		Tyr	Val	Ala	Ile 100	Сув	Phe	Pro	Leu	His 105	Tyr	Thr	Asn	Ile	<b>Met</b> 110	Ser	His
		Lys	Leu	Cys 115	Thr	Cys	Leu	Leu	Leu 120	Val	Phe	Trp	Ile	<b>M</b> et 125	Arg	Ser	Ser
		His	Ala 130	Met	Met	Ile	Thr	Leu 135	Ile	Ala	Ala	Arg	Leu 140	Ser	Phe	Сув	Glu
20		Asn 145	Asn	Val	Leu	Leu	Asn 150	Phe	Phe	Cys	qaA	Leu 155	Phe	Val	Leu	Leu	Lys 160
		Leu	Ala	Сув	Ser	<b>Asp</b>	Thr	Tyr	Val	Asn	Glu 170	Leu	Met	Ile	aiH	Ile 175	Met
25		Glu	Val	Ile	Ile 180	Ile	Val	Ile	Pro	Phe 185	Val	Leu	Ile	Val	Ile 190	Ser	Tyr
		Ala	Lys	Val 195	Pro	Ser	Thr	Gln	Ser 200	Ile	His	Lys	Val	Phe 205	Ser	Thr	Суѕ
		Gly	Ser 210	His	Leu	Ser	Val	<b>Val</b> 215	Ser	Leu	Phe	Tyr	Gly 220	Thr	Ile	Ile	Gly
30		Leu 225	Tyr	Leu	Cys	Pro	Ser 230	Gly	Ąsp	Asn	Phe	Ser 235	Leu	Lys	Gly	Ser	Leu 240
		Thr	Val	Val	Thr	Pro 245	Ile	Met	Pro	Phe	Ile 250	Tyr	Ser	Leu	Arg	Asn 255	Arg
35		Asp	Met	Lys	Gln 260	Ala	Leu	Ile	Arg	Val 265	Thr	Cys	Ser	Lys	Lys 270	Ile	Ser
		Leu	Pro	Trp 275													
40	(2)	(i)	SEQI (A (B (C	ION I UENCI ) LEI ) TYI ) STI ) TOI	E CHANGTH PE: 8 RANDI	ARAC' : 284 amin EDNE:	reris 4 am: 5 ac: SS:	STIC: ino a id sing:	S: acida	5							
<b>1</b> 5			MOL	ECULI	E TY	PE: ]	pept	ide	PO T1	D. N∕O	. 67.						
<b>4</b> 5				UENCI Tyr								Leu	Thr	Thr	Leu	Leu 15	Gly

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	Asn	Leu	Ile	Ile 20	Ile	Ile	Leu	Ile	Leu 25	Leu	Asp	Ser	His	Leu 30	His	Thr
	Pro	Met	Tyr 35	Leu	Phe	Leu	Ser	Asn 40	Leu	Ser	Phe	Ala	Asp 45	Leu	Cys	Phe
5	Ser	Ser 50	Leu	Lys	Leu	Leu	Gln 55	Asn	Met	Gln	Ser	Gln 60	Val	Pro	Ser	Ile
	Pro 65	Tyr	Ala	Gly	Cys	Leu 70	Ala	Gln	Ile	Tyr	Phe 75	Phe	Leu	Phe	Phe	Gly 80
10	ĄaĄ	Leu	Gly	Asn	Phe 85	Leu	Leu	Val	Ala	<b>M</b> et 90	Ala	Tyr	Asp	Arg	Tyr 95	Val
	Ala	Ile	Сув	Phe 100	Pro	Leu	His	Tyr	<b>Met</b> 105	Ser	Ile	Met	Ser	Pro 110	Lys	Ile
	Glx	Val	Ser 115	Leu	Val	Val	Leu	Ser 120	Trp	Val	Leu	Thr	Thr 125	Phe	His	Ala
15	Met	Leu 130	His	Thr	Leu	Ile	Met 135	Ala	Arg	Leu	Ser	Phe 140	Сув	Gl	Asp	Ser
	Val 145	Ile	Pro	His	Tyr	Phe 150	Cys	Asp	Met	Ser	Thr 155	Leu	Leu	Lув	Val	<b>Ala</b> 160
20	Cys	Ser	qaA	Thr	His 165	Asp	Asn	Glu	Leu	Ala 170	Ile	Phe	Ile	Leu	Gly 175	Gly
	Pro	Ile	Val	Val 180	Leu	Pro	Phe	Leu	Leu 185	Ile	Ile	Val	Ser	<b>Tyr</b> 190	Ala	Arg
	Ile	Val	Ser 195	Ser	Ile	Phe	Lys	Val 200	Pro	Ser	Ser	Gln	Ser 205	Ile	His	Lys
25	Ala	Phe 210	Ser	Thr	Cys	Gly	Ser 215	His	Leu	Ser	Val	Val 220	Ser	Leu	Phe	Tyr
	225					Leu 230					235					240
30	Val	Lys	Glu	Thr	Val 245	Met	Ser	Ile	Tyr	Thr 250	Met	Val	Pro	Met	Leu 255	Asn
	Pro	Phe	Ile	Tyr 260	Ser	Leu	Arg	Asn	Arg 265	Asp	Ile	Lys	qaA	Ala 270	Leu	Glu
	Lys	Ile	<b>M</b> et 275	Сув	Lys	Lys	Gln	Ile 280	Pro	Ser	Phe	Leu				
35	(2) INFOR	SEQUAL (A)	JENCE LEN TYP	CHA IGTH: PE: a	RACT 277 mino	D NO PERIS ami aci SS: s	TICS no a ld	S: acids	;							
40	(ii)					inea epti										
	(xi)	SEQU	JENCE	E DES	CRIF	TION	: SE									
	Leu 1	Phe	Tyr	Ala	<b>Le</b> u 5	Phe	Leu	Ala	Met	Tyr 10	Leu	Thr	Ile	Ile	Leu 15	Gly
45	Asn	Leu	Leu	Ile 20	Ile	Val	Leu	Val	Arg 25	Leu	qaA	Ser	His	Leu 30	His	Met

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											_						
	т	уr	Leu	Phe 35	Leu	Ser	Asn	Leu	Ser 40	Phe	Ser	Asp	Leu	Cys 45	Phe	Ser	Ser
	v		Thr 50	Trp	Lys	Leu	Leu	Gln 55	Asn	Met	Gln	Ser	Gln 60	Val	Pro	Ser	Ile
5		er 5	Tyr	Thr	Gly	Сув	Leu 70	Thr	Gln	Leu	Tyr	Phe 75	Phe	Met	Val	Phe	Gly 80
	A	sp	Trp	Ser	Phe	Leu 85	Leu	Val	Val	Met	Ala 90	Tyr	Asp	Arg	Tyr	Val 95	Ala
10	I	le	Cys	Phe	Pro 100	Leu	Arg	Tyr	Thr	Thr 105	Ile	Met	Ser	Thr	Lys 110	Phe	Сув
	A	la	Ser	Leu 115	Val	Leu	Leu	Leu	Trp 120	Met	Leu	Thr	Met	Arg 125	His	Ala	Leu
	L		His 130	Thr	Leu	Leu	Ile	Ala 135	Arg	Leu	Ser	Phe	Cys 140	Glu	Asp	Ser	Val
15		1e 45	Leu	His	Phe	Phe	Cys 150	Asp	Ile	Ser	Ala	Leu 155	Leu	Lys	Leu	Ser	Cys 160
	S	er	Asp	Ile	Tyr	Val 165	Asn	Glu	Leu	Met	Ile 170	Tyr	Ile	Leu	Gly	Gly 175	Leu
20	I	le	Ile	Ile	Ile 180	Pro	Phe	Leu	Leu	Ile 185	Val	Met	Ser	Tyr	Val 190	Arg	Ile
	P	he	Phe	Ser 195	Ile	Leu	Lys	Phe	Pro 200	Ser	Ile	Gln	Asp	Ile 205	Тут	Lys	Val
	P	he	Ser 210	Thr	Cys	Gly	Ser	His 215	Leu	Ser	Val	Val	Thr 220	Leu	Phe	Tyr	Gly
25		hr 225	Ile	Phe	Gly	Ile	Tyr 230	Leu	Cys	Pro	Ser	Gly 235	Asn	Asn	Ser	Thr	Val 240
	I	Lys	Glu	Ile	Leu	Thr 245	Val	Val	Thr	Pro	<b>M</b> et 250	Ile	Asn	Pro	Phe	Ile 255	Tyr
30	S	Ser	Leu	Arg	Asn 260	Arg	Asp	Trp	Arg	Ala 265	Leu	Ile	Arg	Val	Ile 270	Cys	Thr
	I	Lys	Lys	Ile 275	Ser	Leu											
35	(2) IN		SEQ!	ION I UENCI ) LEI ) TYI	E CHI NGTH	ARAC" : 27	reri: 4 am:	STIC:	S:	5							
	( j	ii)	(C	) ST ) TO: ECUL	RAND: POLO	EDNE: GY :	SS:	sing ar	le								
40	7			UENC Tyr								Leu	Thr	Ile	Vaı	Leu 15	Gly
	1	Asn	Leu	Ile	Ile 20	Ile	Ile	Leu	Ile	His 25	Leu	Asp	Ser	His	Leu 30	His	Thr
45	I	Pro	Met	Tyr 35	Leu	Phe	Leu	Ser	Asn 40	Leu	Ser	Phe	Ser	Asp 45	Leu	Cys	Phe

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	Ser	Ser 50	Leu	Lys	Leu	Leu	Gln 55	Asn	Met	Gln	Ser	Gln 60	Val	Pro	Ser	Ile
	Pro 65	Phe	Ala	Gly	Cys	Leu 70	Thr	Gln	Leu	Tyr	Phe 75	Tyr	Leu	Tyr	Phe	Ala 80
5	Asp	Leu	Glu	Ser	Phe 85	Leu	Leu	Val	Ala	<b>M</b> et 90	Ala	Tyr	Asp	Arg	Tyr 95	Val
	Ala	Ile	Cys	Phe 100	Pro	Leu	His	Tyr	Met 105	Ser	Ile	Met	Ser	Pro 110	Lys	Leu
10	Cys	Val	Ser 115	Leu	Trp	Leu	Ser	Trp 120	Val	Leu	Thr	Thr	Phe 125	His	Ala	Met
	Leu	His 130	Thr	Leu	Ile	Met	Ala 135	Arg	Leu	Ser	Phe	Cys 140	Ala	Asp	Leu	Pro
	His 1 <b>4</b> 5	Phe	Phe	Cys	qaA	Ile 150	Ser	Pro	Leu	Leu	Lys 155	Leu	Ser	Cys	Ser	Asp 160
15	Thr	His	Val	naA	Glu 165	Leu	Val	Ile	Phe	Leu 170	Gly	Leu	Val	Ile	Val 175	Ile
	Pro	Phe	Val	Leu 180	Ile	Ile	Val	Ser	Tyr 185	Ala	Arg	Val	Val	Ala 190	Ser	Ile
20	Leu	Lys	Val 195	Pro	Ser	Val	Arg	Gly 200	Ile	His	Lys	Ile	Phe 205	Ser	Thr	Сув
	Gly	Ser 210	His	Leu	Ser	Val	Val 215	Ser	Leu	Phe	Tyr	Gly 220	Thr	Ile	Ile	Gly
	Leu 225	Tyr	Leu	Сув	Pro	Ser 230	Ala	Asn	Asn	Ser	Thr 235	Val	Lys	Glu	Thr	Leu 240
25	Thr	Val	Val	Thr	Pro 245	Leu	Pro	Phe	Ile	Tyr 250	Ser	Leu	Arg	Asn	Arg 255	Asp
	Met	Lys	Glu	Ala 260	Leu	Ile	Arg	Val	Leu 265	Сув	Lys	Lys	Lys	Ile 270	Thr	Phe
30	Cys	Leu														
	(2) INFO	SEQI (A)	ION I JENCI LEI TYI	CHI NGTH	ARAC: 34:	reri:	STIC:	S:	5							
35	(ii)	(C)	STI TOI	RANDI POLO	EDNES	SS: :	sing: ar	le								
40			JENCI Ile								Leu	Gly	Thr	Phe	Thr 15	Val
	Leu	Glu	naA	Leu 20	Leu	Val	Leu	Cys	Val 25	Ile	Leu	His	Ser	Arg 30	Ser	Leu
	Arg	Cys	Arg 35	Pro	Ser	Tyr	His	Phe 40	Ile	Gly	Ser	Leu	Ala 45	Val	Ala	qaA
<b>4</b> 5	Leu	Leu 50	Gly	Ser	Val	Ile	Phe 55	Val	Tyr	Ser	Phe	Val 60	Asp	Phe	His	Val
	Phe 65	His	Arg	Lys	Asp	Ser 70	Pro	Asn	Val	Phe	Leu 75	Phe	Lys	Leu	Gly	Gly 80

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		Val	Thr	Ala	Ser	Phe 85	Thr	Ala	Ser	Val	Gly 90	Ser	Leu	Phe	Leu	Thr 95	Ala
		Ile	Asp	Arg	Tyr 100	Ile	Ser	Ile	His	Pro 105	Pro	Ile	Ala	Tyr	Lys 110	Arg	Ile
5		Val	Arg	Arg 115	Pro	Lys	Ala	Val	Val 120	Ala	Phe	Cys	Leu	Met 125	Thr	Ile	Ala
		Ile	Val 130	Ile	Ala	Val	Leu	Pro 135	Leu	Leu	Gly	Trp	Asn 140	Сув	Lys	Lys	Leu
10		Gln 145	Ser	Val	Сув	Cys	Asp 150	Ile	Phe	Pro	Leu	Ile 155	Asp	Gly	Thr	Tyr	Leu 160
		Met	Phe	Trp	Ile	Gly 165	Val	Thr	Ser	Val	Leu 170	Leu	Leu	Phe	Ile	Val 175	Tyr
		Ala	Tyr	Met	Tyr 180	Ile	Leu	Trp	Lys	Ala 185	His	Ser	His	Ala	Val 190	Arg	Ala
15		Gln	Arg	Gly 195	Thr	Gln	Lys	Ser	Ile 200	Ile	Ile	His	Thr	Ser 205	Glu	Asp	Gly
		Lys	Val 210	Gln	Val	Thr	Arg	Pro 215	qaA	Gln	Ala	Arg	Met 220	Asp	Ile	Arg	Leu
20		Ala 225	Lys	Thr	Leu	Val	Leu 230	Ile	Leu	Val	Val	<b>Leu</b> 235	Ile	Ile	Сув	Trp	Gly 240
		Pro	Leu	Leu	Ala	Ile 245	Met	Val	Tyr	Asp	Val 250	Phe	Gly	Leu	Leu	Ile 255	Lys
		Thr	Val	Phe	Ala 260	Phe	Cys	Ser	Leu	Leu 265	Ile	Asn	Ser	Thr	Val 270	Asn	Pro
25		Ile	Ile	Tyr 275	Ala	Leu	Arg	Ser	Lys 280	Asp	Leu	Arg	His	Ala 285	Phe	Arg	Ser
		Trp	Pro 290	Ser	Сув	Glu	Gly	Thr 295	Ala	Gln	Pro	Leu	<b>Asp</b> 300	Asn	Ser	Met	Gly
30		<b>Asp</b> 305	Ser	Asp	Сув	Leu	His 310	Lys	His	Ala	naA	Asn 315	Thr	Ala	Ser	Met	His 320
		Arg	Ala	Ala	Glu	Ser 325	Сув	Ile	Lys	Ser	Thr 330	Val	Lys	Leu	Ala	Leu 335	Val
		Ser	Thr	qaA	Thr 340	Ser	Ala	Glu	Ala	Leu 345					•		
35	(2)	INFO	SEQI (A (B		E CHA NGTH PE: 6	ARAC : 34:	reris 9 am: o ac:	STIC: ino a id	S: acid:	S							
40		(ii)	MOL.	) TO													
		(xi)	SEQ	UENC	E DE	SCRI	PTIO	N: S	EQ I	ON C	:71:						
		Lys 1	Ala	Leu	Leu	Ile 5	Val	Ala	Tyr	Ser	Phe 10	Thr	Ile	Val	Phe	Ser 15	Leu
45		Phe	Gly	Asn	Val 20	Leu	Val	Cys	His	Tyr 25	Ile	Phe	Lys	Asn	Gln 30	Arg	Lys

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		Ile	e Ser	Ala 35	Thr	Ser	Leu	Phe	Ile 40	. Val	Asn	Leu	Ala	Val 45	Ala	. Asp	Ile
		Ile	Glu 50	Thr	Leu	Leu	Asn	Thr 55	Pro	Phe	Thr	Leu	Val	Arg	Phe	Val	Asn
5		Ser 65	Thr	Trp	Tyr	Phe	Gly 70	Lys	Gly	Met	Leu	His 75	Val	Ser	Arg	Phe	Ala 80
		Gln	Tyr	Cys	Ser	Leu 85	His	Val	Ser	Ala	Leu 90	Ile	Leu	Thr	Ala	Ile 95	Ala
10		Val	Asp	Arg	His 100	Gln	Val	Ile	Met	Pro 105	Leu	Lys	Pro	Arg	Ile 110		Ile
		Thr	Lys	Gly 115	Val	Ile	Tyr	Ile	Ala 120	Val	Ile	Trp	Val	Met 125	Thr	Phe	Phe
		Ser	Leu 130	Pro	His	Ala	Ile	Сув 135	Gln	Lys	Leu	Phe	Thr 140	Phe	Lys	Tyr	Ser
15		Glu 145	Asp	Ile	Val	Arg	Ser 150	Leu	Cys	Leu	Asp	Pro 155	Phe	Pro	Glu	Pro	Ala 160
		Asp	Leu	Phe	Trp	Lys 165	Tyr	Leu	Asp	Ile	Ala 170	Thr	Phe	Ile	Leu	Leu 175	Tyr
20		Leu	Leu	Pro	Leu 180	Phe	Ile	Ile	Ser	Val 185	Ala	Tyr	Ala	Arg	Vai 190	Ala	Lys
		Lys	Leu	Trp 195	Leu	Cys	Asn	Thr	Ile 200	Gly	Asp	Val	Thr	Thr 205	Glu	Gln	Tyr
		Leu	Ala 210	Leu	Arg	Arg	Lys	Lys 215	Lys	Thr	Thr	Val	Lys 220	Met	Leu	Val	Leu
25		Val 225	Val	Val	Leu	Phe	Ala 230	Leu	Cys	Trp	Phe	Pro 235	Leu	Asn	Cys	Tyr	Val 240
		Leu	Leu	Leu	Ser	Ser 245	Lys	Ala	Ile	His	Thr 250	Asn	Asn	Ala	Leu	Tyr 255	Phe
30		Ala	Phe	His	Trp 260	Phe	Ala	Met	Ser	Ser 265	Thr	Cys	Tyr	Asn	Pro 270	Phe	Ile
		Tyr	Cys	Trp 275	Leu	Asn	Glu	Asn	Phe 280	Arg	Val	Glu	Leu	<b>Lув</b> 285	Ala	Leu	Leu
			290		Pro			295					300				
35		Pro 305	Ser	Phe	Arg	Val	Ala 310	Trp	Thr	Glu	Lys	Ser 315	His	Gly	Arg	Arg	Ala 320
		Pro	Leu	Pro	Asn	His 325	His	Leu	Pro	Ser	Ser 330	Gln	Ile	Gln	Ser	Gly 335	Lys
40		Thr	Asp	Leu	Ser 340	Ser	Val	Glu	Pro	Val 345	Val	Ala	Met	Ser			
45	(2)	(i)	SEQU (A) (B) (C) (D)	JENCE LEN TYP STR TOP	CHA IGTH: E: a LANDE OLOG	RACT 301 mino DNES Y: 1	ERIS ami aci S: s inea	TICS no a d ingl	: cids	3							
		(ii)	MOLE	CULE	TYP	E: p	epti	de									

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		(xi)	SEQ	JENCI	E DES	SCRI	PTIO	N: SI	EQ II	OM C	: 72 :						
		Ile 1	Phe	Thr	Ile	Ala 5	Leu	Ala	Tyr	Gly	Ala 10	Val	Ile	Ile	Leu	Gly 15	Val
5		Ser	Gly	Asn	Leu 20	Ala	Leu	Ile	Ile	Ile 25	Ile	Leu	Lys	Gln	Lys 30	Glu	Leu
		Ile	Leu	Ile 35	Val	naA	Leu	Ser	Phe 40	Ser	qaA	Leu	Leu	Val 45	Ala	Val	Trp
		Leu	Pro 50	Phe	Thr	Phe	Val	Тут 55	Thr	Leu	Ile	Сув	His 60	Trp	Val	Phe	Gly
10		Glu 65	Cys	Cys	Lys	Leu	Asn 70	Pro	Phe	Val	Gln	Cys 75	Val	Ser	Ile	Thr	Val 80
		Ser	Ile	Phe	Ser	Leu 85	Val	Leu	Ile	Ala	Val 90	Glu	Arg	His	Gl	Leu 95	Ile
15		Ile	Asn	Pro	Arg 100	Gly	Trp	Arg	Pro	Asn 105	Asn	Arg	His	Ala	Tyr 110	Ile	Gly
		Ile	Thr	Val 115	Ile	Trp	Val	Ile	Ala 120	Val	Ala	Ser	Ser	Leu 125	Pro	Phe	Val
		Ile	Tyr 130	Gln	Ile	Leu	Thr	Asp 135	Glu	Pro	Phe	Gln	Asn 140	Val	Ser	Leu	Ala
20		Ala 145	Phe	Lys	Asp	Lys	Tyr 150	Val	Сув	Phe	Asp	Lys 155	Phe	Pro	Ser	Asp	Ser 160
		His	Arg	Leu	Ser	Tyr 165	Thr	Thr	Leu	Leu	Leu 170	Val	Leu	Gln	Tyr	Phe 175	Gly
25		Pro	Leu	Cys	Phe 180	Ile	Phe	Ile	Cys	Tyr 185	Phe	Lys	Ile	Tyr	Ile 190	Arg	Leu
		Lys	Arg	Arg 195	naA	Asn	Met	Met	<b>Lys</b> 200	Ile	Arg	Asp	Ser	Lys 205	Tyr	Arg	Ser
		Ser	Glu 210	Thr	Lys	Arg	Ile	Asn 215	Val	Met	Leu	Leu	Ser 220	Ile	Val	Val	Ala
30		Phe 225	Ala	Val	Cys	Trp	Leu 230	Pro	Leu	Thr	Ile	Phe 235	Asn	Ile	Va.	Phe	Asp 240
		Trp	naA	His	Gln	Ile 2 <b>4</b> 5	Ile	Ala	Thr	Cys	Asn 250	His	Asn	Leu	Leu	Phe 255	Leu
35		Leu	Сув	His	Leu 260	Thr	Leu	Ser	Thr	Суs 265	Val	Asn	Pro	Ile	Phe 270	Tyr	Gly
		Phe	Leu	Asn 275	Lys	Asn	Phe	Gln	Arg 280	Asp	Leu	Gln	Phe	Phe 285	Phe	Asn	Phe
		Cys	<b>As</b> p 290	Phe	Arg	Ser	Arg	<b>Asp</b> 295	Gly	Arg	Thr	Thr	<b>Ar</b> g 300	Leu			
40	(2)	INFOI (i)	SEQI (A	JENCI LEI TY	E CHA NGTH PE: 8	ARAC : 334 amin	ID NO FERIS 4 am: 5 ac: SS: 5	STIC: ino a id	S: acida	5							
45		(ii)	(D	TO	POLO	GY:	linea	ar									

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	(xi)	SEQ	UENC:	E DE	SCRI	PTIO	N: S	EQ I	D NO	:73:						
	Leu 1	Thr	Ser	Val	Val 5	Phe	Ile	Leu	Ile	Cys 10	Cys	Phe	Ile	Ile	Leu 15	Glu
5	Asn	Ile	Phe	Val 20	Leu	Leu	Thr	Ile	Trp 25	Lys	Thr	Lys	Lys	Phe 30	His	Arg
	Pro	Met	Tyr 35	Tyr	Phe	Ile	Gly	Asn 40	Ile	Ala	Leu	Ser	Asp 45	Leu	Ile	Ala
	Gly	<b>Va</b> l 50	Ala	Tyr	Thr	Ala	Asn 55	Leu	Leu	Leu	Ser	Gly 60	Ala	Thr	Thr	Tyr
10	Lys 65	Leu	Thr	Pro	Ala	Gln 70	Trp	Phe	Leu	Arg	Glu 75	Gly	Ser	Met	Phe	Val 80
	Ala	Leu	Ser	Leu	Ser 85	Val	Phe	Ser	Leu	Leu 90	Ala	Ile	Ala	Ile	Glu 95	Arg
15	Tyr	Ile	Thr	Met 100	Leu	Lys	Met	Leu	His 105	Asn	Gly	Ser	Asn	Asn 110	Phe	Arg
	Leu	Phe	Leu 115	Leu	Ile	Ser	Ala	Cys 120	Trp	Val	Ile	Ser	Leu 125	Ile	Leu	Gly
	Gly	Leu 130	Pro	Ile	Met	Gly	Trp 135	Asn	Cys	Ile	Ser	Ala 140	Leu	Ser	Ser	Сув
20	Ser 145	Thr	Val	Leu	Pro	Leu 150	Tyr	His	Lys	His	Tyr 155	Ile	Leu	Phe	Cys	Thr 160
	Leu	Ile	Val	Phe	Thr 165	Leu	Leu	Leu	Leu	Ser 170	Ile	Val	Ile	Leu	Tyr 175	Cys
25	Arg	Ile	Tyr	Ser 180	Leu	Val	Arg	Thr	Arg 185	Ser	Arg	Arg	Leu	Thr 190	Phe	Arg
	Lys	Asn	Ile 195	Ser	Lys	Ala	Ser	<b>A</b> rg 200	Ser	Ser	Glu	Asn	Val 205	Ala	Leu	Leu
		210					215					220		Trp		
30	225					230					235			Lys		240
					245					250				Val	255	
35	Ser	Gly	Thr	Asn 260	Pro	Ile	Ile	Tyr	Thr 265	Leu	Thr	Asn	Lys	Glu 270	Met	Arg
	Arg	Ala	Phe 275	Ile	Arg	Ile	Met	Cys 280	Cys	Lys	Cys	Pro	Ser 285	Gly	Asp	Ser
	Ala	Gly 290	Lys	Phe	Lys	Arg	Pro 2 <b>9</b> 5	Ile	Ile	Ala	Gly	Met 300	Glu	Phe	Ser	Arg
40	Ser 305	Lys	Ser	Asp		Ser 310	Ser	His	Pro	Gln	Lys 315	Asp	Glu	Gly	Asp	Asn 320
	Pro	Glu	Thr		<b>M</b> et 325	Ser	Ser	Gly	Asn	Val 330	Asn	Ser	Ser	Ser		

- (2) INFORMATION FOR SEQ ID NO:74:
  (i) SEQUENCE CHARACTERISTICS:
  (A) LENGTH: 236 amino acids 45

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		(ii)	(C (D	TOI	RANDI POLO	EDNE:	SS: s linea	sing: ar	le								
5		(xi) Ile 1					PTIOI Leu					Ala	Val	Val	Gly	Asn 15	Ile
		Leu	Leu	Val	Ile 20	Trp	Val	Val	Lys	Leu 25	Asn	Arg	Thr	Leu	Arg 30	Thr	Thr
10		Thr	Phe	Tyr 35	Phe	Ile	Val	Ser	Ile 40	Ala	Leu	Ala	qaA	Ile 45	Ala	Val	Leu
		Val	Ile 50	Pro	Leu	Ala	Ile	Ala 55	Ser	Ala	Trp	Arg	Ser 60	Arg	Суѕ	Thr	Ser
15		Asn 65	Cys	Leu	Phe	Met	Ser 70	Cys	Val	Leu	Leu	Val 75	Phe	Thr	His	Ala	Ser 80
		Ile	Met	Ser	Leu	Leu 85	Ala	Ile	Ala	Val	<b>As</b> p 90	Arg	Tyr	Leu	Arg	Val 95	Lys
		Leu	Thr	Val	Arg 100	Tyr	Arg	Thr	Val	Thr 105	Thr	Gln	Arg	Arg	Ile 110	Trp	Leu
20		Phe	Leu	Gly 115	Leu	Сув	Trp	Leu	Val 120	Ser	Phe	Leu	Val	Gly 125	Leu	Thr	Pro
		Trp	Gly 130	Trp	Asn	Arg	Lys	<b>Val</b> 135	Thr	Leu	Glu	Leu	Ser 140	Gln	Asn	Ser	Ser
25		Thr 145	Leu	Arg	Glu	Phe	Lys 150	Thr	Pro	Lys	Ser	Leu 155	Phe	Leu	Val	Leu	Phe 160
						165	Trp			,	170					175	
		Tyr	Phe	Asn	Val 180	Lys	Ile	Pro	Glu	Thr 185	Leu	Leu	Gly	Ile	Leu 190	Leu	Ser
30				195			Pro		200	_		-	-	205	-		-
		Glu	Thr 210	Tyr	Phe	Val	Ile	Leu 215	Arg	Ala	Cys	Arg	Leu 220	Cys	Gln	Thr	Ser
35		<b>Asp</b> 225		Leu	_		Asn 230		Glu	Gln	Thr	Thr 235	Glu				
	(2)	INFOI (i)	SEQUAL (A)	JENCI LEI	GTH:	1RAC	ID NO TERIS 2 aumi 5 a.c.:	STICS ino a	3:	3							
40		(ii)	(D)	TOI	POLO	3Y: ]	SS: s linea pept:	ar	le								
45							PTIOI Phe					Cys	Leu	Val	Gly	Leu 15	Cys
		Gly	Asn	Ser	<b>Me</b> t 20	Val	Ile	Tyr	Val	Ile 25	Leu	Arg	Tyr	Ala	Ly-	Met	Lys
		Thr	Ala	Thr	Asn	Ile	Tyr	Ile	Leu	Asn	Ile	Ala	Ile	Ala	Asp	Glu	Leu

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				35					40					45			
		Leu	Val 50	Pro	Phe	Leu	Val	Thr 55	Ser	Thr	Leu	Leu	Arg 60	His	Trp	Pro	Ph
5		Gly 65	Ala	Leu	Leu	Cys	Arg 70	Leu	Val	Leu	Ser	<b>Val</b> 75	Asp	Ala	Val	Asn	<b>M</b> e1
		Phe	Thr	Ser	Ile	Tyr 85	Суѕ	Leu	Thr	Val	Leu 90	Ser	Val	Asp	Arg	Tyr 95	Va:
		Ala	Val	Val	His 100	Pro	Ile	Lys	Ala	<b>Ala</b> 105	Arg	Tyr	Arg	Arg	Pro		Va
10		Ala	Lys	Val 115	Val	Asn	Leu	Gly	Val 120	Trp	Val	Leu	Ser	Leu 125	Leu	Val	Ile
		Leu	Pro 130	Ile	Trp	Phe	Ser	Arg 135	Thr	Ala	Ala	Asn	Ser 140		Gly	Thr	Va]
15		Ala 145	Сув	Asn	Met	Ile	Trp 150	Glu	Pro	Ala	Gln	Phe 155	Trp	Leu	Va≟	Gly	Phe 160
		Val	Leu	Tyr	Thr	Phe 165	Leu	Met	Phe	Leu	Leu 170	Pro	Val	Gly	Ala	Ile 175	Суз
		Leu	Сув	Tyr	Val 180	Leu	Ile	Ile	Ala	Lys 185	Met	Arg	Met	Val	Ala 190	Leu	Lys
20				195		Gln			200					205			
			210			Met		215					220				
25		225				Phe	230					235					240
						Gly 245					250					255	
					260	qaA				265					270		_
30				275		Ala			280					285			
			290			Ala		295					300				
35		Glu 305	Ser	Gly	Gly	Val	Phe 310	Arg	Asn	Cys	Thr	Cys 315	Ala	Ser	Arg	Ile	Ser 320
		Thr	Leu														
40	(2)		(A) (B) (C)	ENCE LEN TYP STR	CHA GTH: E: a ANDE	EQ I RACT 298 mino DNES	ERIS ami aci S: s	TICS no a d ingl	: cids								
		(ii)															
45		(xi) Val 1	SEQU Thr	ENCE Asn	DES Tyr	CRIP Ile 5	TION Phe	: SE Leu	Q ID Leu	NO: Leu	76: C <b>ys</b> 10	Leu	Cys	Gly	L€u	Val 15	Gly

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		Asn	Gly	Leu	Val 20	Leu	Trp	Phe	Phe	Gly 25	Phe	Ser	Ile	Lys	Arg 30	Thr	Pro
		Phe	Ser	Ile 35	Tyr	Ile	Tyr	Phe	Leu 40	His	Ile	Ala	Ser	Ala 45	Asp	Gly	Ile
5		Tyr	Leu 50	Phe	Ser	Lys	Ala	Val 55	Ile	Ala	Leu	Leu	Asn 60	Met	Gly	Thr	Phe
		Leu 65	Gly	Ser	Phe	Pro	Asp 70	Tyr	Val	Arg	Arg	Val 75	Ser	Arg	Ile	Val	Gly 80
10		Leu	Thr	Phe	Phe	Ala 85	Gly	Val	Ser	Leu	Leu 90	Pro	Ala	Ile	Ser	Ile 95	Glu
		Arg	Cys	Val	Ser 100	Val	Ile	Phe	Pro	<b>Met</b> 105	Trp	Tyr	Trp	Arg	Arg 110	Arg	Pro
		Lys	Arg	Leu 115	Ser	Ala	Gly	Val	Cys 120	Ala	Leu	Leu	Trp	Leu 125	Leu	Ser	Phe
15		Leu	Val 130	Thr	Ser	Ile	His	<b>Asn</b> 135	Tyr	Phe	Cys	Leu	Leu 140	Gly	His	Glu	Ala
		Ser 145	Gly	Thr	Ala	Cys	Leu 150	Asn	Met	Asp	Ile	Ser 155	Leu	Leu	Gly	Ile	Leu 160
20		Leu	Phe	Phe	Leu	Phe 165	Сув	Pro	Ile	Met	Val 170	Leu	Pro	Cys	Ile	Ala 175	Leu
		Leu	His	Val	Glu 180	Сув	Arg	Ala	Arg	Arg 185	Arg	Gln	Arg	Ser	Ala 190	Lys	Leu
		Asn	His	Val 195	Val	Leu	Ala	Ile	Val 200	Ser	Val	Phe	Leu	Val 205	Ser	Ser	Ile
25		Tyr	Leu 210	Gly	Ile	Asp	Trp	Phe 215	Leu	Phe	Trp	Val	Phe 220	Gln	Ile	Pro	Ala
		Pro 225	Phe	Pro	Glu	Tyr	Val 230	Arg	qaA	Leu	Cys	Ile 235	Сув	Ile	Asn	Ser	Ser 240
30		Ala	Lys	Pro	Ile	Val 245	Tyr	Phe	Ile	Ala	Gly 250	Arg	Asp	Lys	Ser	Gln 255	Arg
		Leu	Trp	Glu	Pro 260	Leu	Arg	Val	Val	Phe 265	Gln	Arg	Ala	Leu	Arg 270	Asp	Gly
		Ala	Glu	Pro 275	Gly	Asp	Ala	Ala	Ser 280	Ser	Thr	Pro	Asn	Thr 285	۷a۱	Thr	Met
35		Glu	<b>M</b> et 290	Gln	Cys	Pro	Ser	Gly 295	Asn	Ala	Ser						
40	(2)	INFO	SEQU (A) (B) (C)	JENCI LEI TYI STI	E CHI NGTH PE: 8 RANDI	ARAC: 299 amino EDNES	ID NO FERIS am: cac: SS: s line	STICS ino a id sing:	S: acid:	5							
		(ii)	MOLI	CULI	E TYI	PE: F	pept:	ide									
45		(xi) Thr 1					PTIOI Leu					Ile	Phe	Val	Gly	Gly 15	Pro
		Ala	Ile	Val	Leu	Ile	Thr	Gln	Leu	Leu	Thr	Asn	Arg	Val	Leu	Gly	Tyr

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					20					25					30		
		Ser	Thr	Pro 35	Thr	Ile	Tyr	Met	Arg 40	Asn	Leu	Tyr	Ser	Thr 45	Asn	Phe	Leu
5		Thr	Leu 50	Thr	Val	Leu	Pro	Phe 55	Ile	Val	Leu	Ser	Asn 60	Gln	Trp	Leu	Leu
		Pro 65	Ala	Cys	Tyr	Val	Ala 70	Ser	Cys	Lys	Phe	Leu 75	Ser	Val	Ile	Tyr	Tyr 80
		Ser	Ser	аұЭ	Thr	<b>Val</b> 85	Gly	Phe	Ala	Thr	Val 90	Ala	Leu	Ile	Ala	Ala 95	qaA
10		Arg	Tyr	Arg	Val 100	Leu	His	Lys	Arg	Thr 105	Tyr	Ala	Arg	Gln	Ser 110	Tyr	Arg
		Ser	Leu	Leu 115	Leu	Thr	Trp	Leu	Ala 120	Gly	Leu	Ile	Phe	Ser 125	Val	Pro	Ala
15		Ala	Val 130	Tyr	Thr	Thr	Val	Val 135	Met	His	His	Asp	Ala 140	Asn	Asp	Thr	Asn
		Asn 145	Thr	Asn	Gly	His	Ala 150	Thr	Cys	Val	Leu	Tyr 155	Phe	Val	Ala	Glu	Glu 160
		Val	His	Thr	Val	Leu 165	Leu	Ser	Trp	Lys	Val 170	Leu	Leu	Thr	Met	<b>Val</b> 175	Trp
20		Gly	Ala	Ala	Pro 180	Val	Ile	Leu	Phe	Tyr 185	Ala	Phe	Phe	Tyr	Se∽ 190	Thr	Val
		Gln	Arg	Thr 195	Ser	Gln	Lys	Gln	Arg 200	Ser	Arg	Thr	Leu	Thr 205	Phe	Val	Ser
25		Val	Leu 210	Leu	Ile	Ser	Phe	Val 215	Ala	Leu	Gln	Thr	Pro 220	Tyr	Val	Ser	Leu
		<b>M</b> et 225	Ile	Phe	Asn	Ser	Tyr 230	Ala	Thr	Thr	Ala	Trp 235	Pro	Met	Cys	Glu	His 240
		Leu	Thr	Leu	Arg	Arg 245	Thr	Ile	Gly	Thr	Leu 250	Ala	Arg	Val	Val	Pro 255	His
30		Leu	His	Cys	Leu 260	Ile	Asn	Pro	Ile	Leu 265	Tyr	Ala	Leu	Leu	Cys 270	His	Asp
		Phe	Leu	Gln 275	Arg	Met	Arg	Gln	Cys 280	Phe	Arg	Gly	Gln	Leu 285	Ile	qaA	Arg
35		Ala	Phe 290	Leu	Arg	Ser	Gln	Gln 295	Asn	Gln	Arg	Ala					
40	(2)	INFOI (i)	SEQUAL (A)	JENCI LEI TYI	E CHA NGTH PE: 8	ARAC : 28:	reris am: ac:	STICS ino a id	S: acida	5							
40		(ii)	(D)	TOI	OLO	<b>3Y</b> : .	SS: s linea pept:	ar	re								
45		(xi) Leu 1					PTIOI <b>M</b> et					Phe	Leu	Leu	Val	Ile 15	Thr
		Thr	Ile	Leu	Tyr 20	Туг	Arg	Arg	Lys	Lys 25	Lys	Ser	Pro	Ser	Asp 30	Thr	Tyr

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		Ile	Cys	<b>Asn</b> 35	Leu	Ala	Val	Ala	Asp 40	Leu	Leu	Ile	Val	Val 45	Gly	Leu	Pro
		Phe	Phe 50	Leu	Glu	Tyr	Ala	Lys 55	His	His	Pro	Lys	Leu 60	Ser	Arg	Glu	Val
5		Val 65	Суѕ	Ser	Gly	Leu	Asn 70	Ala	Cys	Phe	Tyr	Ile 75	Cys	Leu	Phe	Ala	Gly 80
		Val	Cys	Phe	Leu	Ile 85	Asn	Leu	Ser	Met	Asp 90	Arg	Tyr	Cys	Val	Ile 95	Val
10		Trp	Gly	Val	Glu 100	Leu	Asn	Arg	Val	Arg 105	Asn	Asn	Lys	Arg	Ala 110	Thr	Cys
		Trp	Val	Val 115	Ile	Phe	Trp	Ile	Ile 120	Ala	Val	Leu	Met	Gly 125	Met	Pro	His
		Tyr	Ile 130	Met	Tyr	Ser	His	Thr 135	Asn	Asn	Glu	Cys	Val 140	Gly	Trp	Phe	Ala
15		Asn 145	Glu	Thr	Ser	Cys	Trp 150	Phe	Pro	Val	Phe	Leu 155	Asn	Thr	Ly.	Val	Asn 160
		Ile	Cys	Gly	Tyr	Leu 165	Ala	Pro	Ile	Ala	Leu 170	Met	Ala	Tyr	Tyr	Asn 175	Arg
20		Met	Val	Arg	Phe 180	Ile	Ile	Asn	Tyr	Val 185	Gly	Lys	Trp	Phe	<b>M</b> et 190	Gln	Thr
		Leu	His	Val 195	Leu	Leu	Val	Val	Val 200	Val	Ser	Phe	Ala	Ser 205	Phe	Trp	Phe
		Pro	Phe 210	Asn	Leu	Ala	Leu	Phe 215	Leu	Glu	Ser	Ile	Arg 220	Leu	Ile	Ala	Gly
25		Val 225	Tyr	Asn	Asp	Thr	Leu 230	Gln	Asn	Val	Ile	Ile 235	Phe	Cys	Leu	Tyr	Val 240
		Gly	Gln	Phe	Ile	Ala 245	Tyr	Val	Arg	Ala	Cys 250	Leu	Asn	Pro	Gly	Ile 255	Tyr
30		Ile	Leu	Val	Cys 260	Thr	Trp	Phe	Leu	Arg 265	Val	Phe	Ala	Сув	Cys 270	Cys	Val
		Lys	Gln	Glu 275	Ile	Pro	Tyr	Gln	Asp 280	Ile	qaA	Ile		•			
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40		Pro	SEQ Val								Val	Phe	Leu	Phe	Gly		Ile
		l Gly	Asn	Phe		5 Val	Ile	Phe	Thr		10 Thr	Trp	Arg	Arg		15 Ile	Gln
45		Cys	Ser		Asp	Val	Tyr	Phe		25 Asn	Leu	Ala	Ala		30 Asp	Leu	Leu
		Phe	Val	35 Cys	Thr	Leu	Pro	Leu	40 Trp	Met	Gln	Tyr	Leu	45 Leu	Asç	His	Asn

			50					55					60				
		Ser 65	Leu	Ala	Ser	Leu	Ile 70	Pro	Cys	Thr	Leu	Leu 75	Thr	Ala	Cys	Phe	Tyr 80
5		Val	Ala	Ile	Thr	Ala 85	Ser	Leu	Сув	Phe	Ile 90	Thr	Glu	Ile	Ala	Leu 95	Ile
		qaA	Arg	Tyr	Tyr 100	Ala	Ile	Val	Tyr	Met 105	Arg	Tyr	Arg	Pro	Val 110	Lys	Ile
		Gln	Ala	Сув 115	Leu	Phe	Ser	Ile	Phe 120	Trp	Trp	Ile	Phe	Ala 125	Val	Ile	Ile
10		Ala	Ile 130	Pro	His	Phe	Met	Val 135	Val	Ile	Thr	Lys	Lys 140	qaA	Asn	Gln	Cys
		Met 145	Thr	qaA	Tyr	Asp	Tyr 150	Leu	Glu	Val	Ser	Tyr 155	Pro	Ile	Ile	Leu	Asn 160
15		Val	Glu	Leu	Met	Leu 165	Gly	Ala	Phe	Val	Ile 170	Pro	Leu	Ser	Val	Ile 175	Ser
		Tyr	Cys	Tyr	Tyr 180	Arg	Ile	Ser	Arg	Ile 185	Val	Ala	Val	Ser	Gln 190	Ser	Arg
		His	Lys	Gly 195	Arg	Ile	Val	Arg	Val 200	Leu	Ile	Ala	Trp	Leu 205	Val	Phe	Ile
20		Ile	Phe 210	Trp	Leu	Pro	Tyr	His 215	Leu	Thr	Leu	Phe	Val 220	<b>As</b> p	Thr	Ile	Ile
		Lys 225	Leu	Leu	Lys	Trp	Ile 230	Ser	Ser	Ser	Cys	Glu 235	Phe	Glu	Arg	Ser	Leu 240
25		Lys	Arg	Ala	Leu	Ile 245	Leu	Thr	Glu	Ser	Leu 250	Ala	Phe	Cys	His	Cys 255	Cys
		Leu	Asn	Pro	Leu 260	Leu	Tyr	Val	Phe	Val 265	Ile	Gly	Thr	Lys	Phe 270	Arg	Lys
		Asn	Tyr	Thr 275	Val	Cys	Trp	Pro	Ser 280	Phe	Ala	Ser	Asp	Ser 285	Phe	Pro	Ala
30		Met	Tyr 290	Pro	Gly	Thr	Arg	Ala 295									
35	(2)		SEQI (A)	UENC	E CHI	ARAC	ID NO TERIS amin	STIC:	S:								
		(ii)	(D	TO:	POLO	GY:	SS: : line: pept:	ar	le								
40							PTIO					Asp	Trp	Ile	Gly	Tyr 15	Leu
		Asn	Ser	Ile	Ser 20	Met	Val	Ile	Tyr	Thr 25	Leu	Phe	Lys	Lys	Lys 30	Lys	
45	(2)	INFO	SEQ (A (B	UENC: ) LE	E CH NGTH PE:	ARĀC : 34 amin	ID No TERI: ami: o ac: SS:	STIC no a id	S: cids								

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(D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:81: Asp Asp Asp Asn Ile Trp Asn Ile Phe Ser Thr Ile Gly Tyr Leu Asn Ser Ile Ser Pro Val Ser Val Ile Met His Ile Tyr Gly Lys Lys Lys Lys (2) INFORMATION FOR SEQ ID NO:82: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 29 amino acids (B) TYPE: amino acid
(C) STRANDEDNESS: single 15 (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:82: Asp Asp Asp Asp Gly Tyr Ser Ile Tyr Asp Thr Leu Val Thr Phe Ala 20 Ile Asn Pro Val Tyr Ile Thr Val Phe Lys Lys Lys 20 (2) INFORMATION FOR SEQ ID NO:83: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 31 amino acids (B) TYPE: amino acid
(C) STRANDEDNESS: single 25 (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:83: 30 Asp Asp Asp Asn Ala Trp Ser Ala Phe Asp Trp Ala Leu Tyr Leu Asn Ser Ile Ser Met Ala Ile Tyr Thr Tyr Ala Lys Lys Lys 20 25 (2) INFORMATION FOR SEQ ID NO:84: 35 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 23 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 40 (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:84: Leu Phe Ser Phe Ile Thr Trp Leu Gly Tyr Ala Asn Ser Ser Leu Asn 10 Pro Ile Ile Tyr Thr Thr Phe 45 20 (2) INFORMATION FOR SEQ ID NO:85: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 23 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 50 (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:85: Tyr Thr Ile Tyr Ser Ser Ser Val Val Phe Phe Ala Pro Ser Leu Ala 55 10 Ile Met Val Ile Thr Tyr Thr

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(2) INFORMATION FOR SEQ ID NO:86:
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               (B) TYPE: amino acid
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               (C) STRANDEDNESS: single
               (D) TOPOLOGY: linear
         (ii) MOLECULE TYPE: peptide
         (xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:
          Ile Trp Leu Thr Ser Asp Ile Met Ser Thr Ser Ser Ile Leu His Asn
10
          Leu Cys Val Ile Ser Phe
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15
               (A) LENGTH: 30 amino acids
               (B) TYPE: amino acid
               (C) STRANDEDNESS: single (D) TOPOLOGY: linear
         (ii) MOLECULE TYPE: peptide
         (xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:
20
          Ile Trp Ser Ile Phe Ser Ser Asp Ile Val Val Gly Tyr Ala Asn His
          Ser Ser Leu Ala Ile Met Cys Pro Ile Val Ile Tyr Thr Va
                                            25
25
    (2) INFORMATION FOR SEQ ID NO:88:
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                (A) LENGTH: 29 amino acids
                (B) TYPE: amino acid
               (C) STRANDEDNESS: single
30
               (D) TOPOLOGY: linear
         (ii) MOLECULE TYPE: peptide
         (xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:
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          Ser Ser Ala Ala Ile Met Pro Ile Val Ile Tyr Ser Val
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                (A) LENGTH: 24 amino acids
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                (B) TYPE: amino acid
               (C) STRANDEDNESS: single (D) TOPOLOGY: linear
         (ii) MOLECULE TYPE: peptide
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          Lys Asn Ala Ser Ala Leu Leu Ser Val Ile Ile Ile Asn Ser Ile Gly
45
                                                10
                           5
          Gly Asn Val Val Thr Ala Val Ser
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50
                (A) LENGTH: 22 amino acids
                (B) TYPE: amino acid
                (C) STRANDEDNESS: single
         (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide
55
         (xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:
          Tyr Phe Leu Met Ser Leu Ala Val Thr Asp Leu Val Val Ser Phe Val
                                                10
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Met Pro Val Ser Ala Leu
20
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(2) INFORMATION FOR SEQ ID NO:91: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 23 amino acids 5 (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91: 10 Ala Ile Thr Lys Ile Ala Ile Thr Trp Ala Ile Ser Gly Val Ser Val 10 Pro Phe Ile Pro Val Trp Gly 20 15 (2) INFORMATION FOR SEQ ID NO:92: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 24 amino acids (B) TYPE: amino acid(C) STRANDEDNESS: single 20 (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:92: Leu Gly Ile Ile Phe Gly Thr Phe Ile Ile Ile Trp Leu Pro Phe Phe 25 Ile Thr Asn Leu Val Ser Pro Ile 20 (2) INFORMATION FOR SEQ ID NO:93: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 23 amino acids(B) TYPE: amino acid(C) STRANDEDNESS: single 30 (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:93: Ile Trp Ile Ser Leu Asp Val Leu Phe Ser Thr Ala Ser Ser Ile Met 35 5 10 His Leu Cys Ala Ile Ser Leu 20 (2) INFORMATION FOR SEQ ID NO:94: (i) SEQUENCE CHARACTERISTICS: 40 (A) LENGTH: 23 amino acids (B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide 45 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:94: Gly Tyr Thr Ile Tyr Ser Thr Leu Val Thr Phe Tyr Ile Pro Ser Val 10 Ile Met Val Ile Thr Tyr Gly 50 20 (2) INFORMATION FOR SEQ ID NO:95: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 23 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single
(D) TOPOLOGY: linear 55 (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

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Leu Leu Asn Phe Phe Asn Trp Ile Gly Tyr Leu Asn Ser Leu Ile Asn 1 10 15

Pro Val Ile Tyr Thr Leu Phe 20

## WHAT IS CLAIMED IS:

- 1. A G-protein coupled receptor polypeptide, consisting essentially of an amino acid sequence of 15 to 40 amino acids substantially corresponding to a fragment or consensus peptide of a transmembrane domain of a G-protein coupled receptor, wherein said polypeptide has a GPR-related biological activity selected from binding a GPR ligand or modulating GPR ligand binding to a GPR.
- A polypeptide according to claim 1, wherein said polypeptide is selected from a synthetic polypeptide, a recombinant 10 polypeptide or a purified polypeptide.
- 3. A polypeptide according to claim 1, wherein said G-protein coupled receptor is a receptor selected from a cAMP receptor, an adenosine receptor, a  $\beta$ -adrenergic receptor, a muscarinic acetylcholine receptor, an  $\alpha$ -adrenergic receptor, a serotonin receptor, a histamine H2 receptor, a thrombin receptor, a kinin receptor, a follicle stimulating hormone receptor, an opsin, a rhodopsin, an odorant receptor, a cytomegalovirus receptor, or a mas oncogene GPR.
- 4. A polypeptide according to claim 1, wherein said 20 transmembrane domain is selected from at least one of transmembrane domain TM1, TM2, TM3, TM4, TM5, TM6 or TM7.
  - 5. A polypeptide according to claim 3, wherein said transmembrane domain is a  $D_2$  receptor transmembrane segment III or segment V.
- 25 6. A polypeptide according to claim 4, wherein said polypeptide has the amino acid sequence of Fig. 2 (SEQ ID NO:2).
  - 7. A polypeptide according to claim 4, wherein said polypeptide has the amino acid sequence of Fig. 3 (SEQ ID NO:3).
- 8. A polypeptide according to claim 4, wherein said 30 polypeptide has an amino acid sequence selected from one of SEQ ID NOS:80-95.
  - 9. A polypeptide according to claim 4, wherein said polypeptide has an amino acid sequence of one of SEQ ID NOS:96-348.
- 10. A polypeptide according to claim 9, wherein said polypeptide has an amino acid sequence from one of SEQ ID NOS:96-225.

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- 11. A polypeptide according to claim 9, wherein said polypeptide has an amino acid sequence from one  $c\bar{r}$  SEQ ID NOS:226-289.
- 12. A polypeptide according to claim 9, wherein said 5 polypeptide has an amino acid sequence from one of SEQ ID NOS:290-297.
  - 13. A polypeptide according to claim 9, wherein said polypeptide has an amino acid sequence from one of SEQ ID NOS:298-324.
- 14. A polypeptide according to claim 9, wherein said polypeptide has an amino acid sequence from one of SEQ ID NOS:325-338.
- 15. A polypeptide according to claim 9, wherein said polypeptide has an amino acid sequence from one of SEQ ID NOS:339-15 348.
  - 16. A polypeptide according to claim 3, wherein said transmembrane domain is a dopamine receptor transmembrane domain selected from the group consisting of a  $D_1$ ,  $D_2$ ,  $D_3$ ,  $D_4$  or  $D_5$  transmembrane domain.
- 20 17. A composition comprising a polypeptide according to claim 1, or a pharmaceutically acceptable ester, ether, sulfate, carbonate, glucuronide or salt thereof, and a pharmaceutically acceptable carrier.
- 18. A composition according to claim 16, wherein said 25 transmembrane domain is  $D_2$  receptor transmembrane segment III or segment V.
- 19. A composition according to claim 18, further comprising a drug selected from a phenothiazine derivative, a thioxanthine derivative, a butyrophenone derivative, a 30 dihydroindolone, a dibenzoxazepine derivative and an atypical neuroleptic.
- 20. A method for treating a subject suffering from a pathology related to an abnormality of a G-protein coupled receptor, comprising administering to said subject a therapeutically effective amount of composition according to claim 16.
  - 21. The method of claim 20, wherein said pathology is a psychotic disorder.

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22. The method of claim 21, wherein said psychotic disorder is a schizophrenia.

- 23. The method of claim 20, wherein said composition is administered to provide said polypeptide, fragment or consensus 5 peptide thereof, in an amount ranging from about 0.01  $\mu$ g to 100 mg/kg per day.
  - 24. The method of claim 23, wherein said composition is administered to provide said polypeptide, fragment or consensus peptide thereof, in an amount ranging from about  $10\,\mu\mathrm{g}$  to  $10\,\mathrm{mg/kg}$  per day.

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- 25. The method of claim 20, wherein said administering is by oral, mucosal, intravenous, intramuscular or parenteral administration.
- 26. A method for producing a polypeptide according to 15 claim 1, wherein said polypeptide is a recombinant polypeptide obtained from a recombinant host which expresses a heterologous nucleic acid encoding said polypeptide, comprising the steps of:
  - (A) providing a host comprising a recombinant nucleic acid encoding a polypeptide according to claim 1 in expressible form;
  - (B) culturing said host under conditions such that said polypeptide is expressed in recoverable amounts; and
  - (C) recovering said polypeptide produced by said host.
  - 27. The method of claim 26, further comprising:
    - (D) purifying said polypeptide.
  - 28. The method of claim 26, wherein said host is a bacteria or a eukaryotic cell.
- 29. The method of claim 28, wherein said eukaryotic cell 30 is a mammalian cell, an insect cell or a yeast cell.
  - 30. A method for producing a polypeptide according to claim 1, comprising:
  - $\hbox{$(A)$ chemically synthesizing a polypeptide according to claim 1 in recoverable amounts; and}\\$
- 35 (B) recovering said polypeptide.

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31. A method for isolating a G-protein coupled receptor, fragment or consensus sequence thereof, or a protein that binds the G-protein coupled receptor, comprising

- (A) providing a bound support, said support being bound to a polypeptide according to claim 1, or an antibody, anti-idiotype antibody, or a fragment thereof;
- (B) contacting a sample containing said G-protein coupled receptor or said protein that binds a G-protein coupled receptor to said bound support, such that said receptor or protein is reversibly bound to said bound support; and
- (C) recovering said receptor or protein that is attached to the bound support by dissociating the receptor or protein under conditions that cause elution or dissociation of the receptor or protein from said bound support.
- 32. A method according to claim 31, wherein said GPR is a dopamine receptor.
- 33. An antibody, anti-idiotype antibody or a fragment of said antibody or anti-idiotype antibody, that specifically displays an epitope of a G-protein coupled receptor polypeptide, according to claim 1.
- 34. A recombinant nucleic acid comprising a nucleotide sequence encoding a G-protein coupled receptor polypeptide according to claim 1.
  - 35. A vector comprising a nucleic acid according to claim 34.
    - 36. A host cell comprising the nucleic acid of claim 34.
- 37. A host cell according to claim 36, wherein said host cell is selected from a mammalian cell, a yeast cell, a bird cell or an insect cell.
- 38. A host cell according to claim 36, wherein, when said nucleic acid is expressed as said receptor polypeptide in said host cell, a receptor binding molecule comprising said *env* binding domain binds to said receptor polypeptide.

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- 39. A host cell according to claim 37, wherein said host cell is a mammalian cell selected from a human cell, a primate cell or a rodent cell.
- 40. A method for isolating a protein that binds a 5 G-protein coupled receptor, comprising

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- (A) providing a bound support, said support being bound to a polypeptide according to claim 1, or anti-idiotype antibody thereto;
- (B) contacting a sample containing said protein that binds a G-protein coupled receptor to said bound support, such that said protein is reversibly bound to said bound support; and
- (C) recovering said protein that is attached to the bound support by dissociating the receptor or protein under conditions that cause elution or dissociation of the protein from said bound support.
- 41. A method according to claim 40, wherein said GPR is a dopamine receptor.

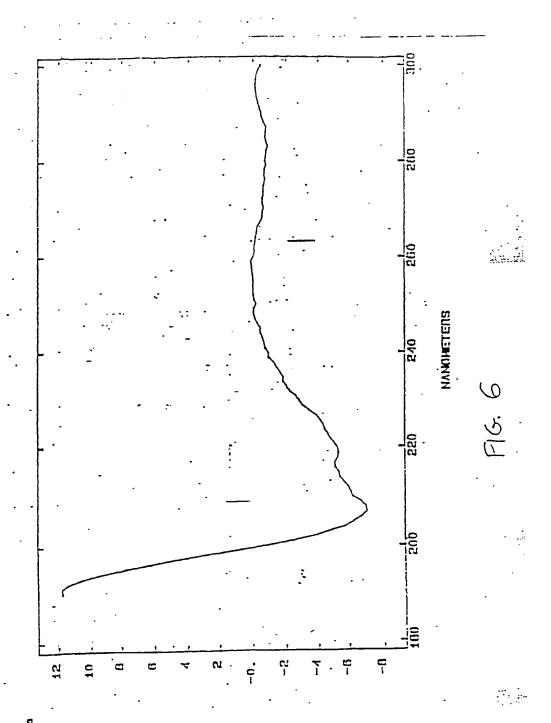
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# DDIFVTLDVLFSTASILNLSAISLKKK

### DYAIFVLYASAWLSFNCPFIVTLNIK

KAVVYSSIVSFTVFID

# DCDVFVFVDIMLCTASIFNLCAISVGK



canc7a

KITTIDESHEES

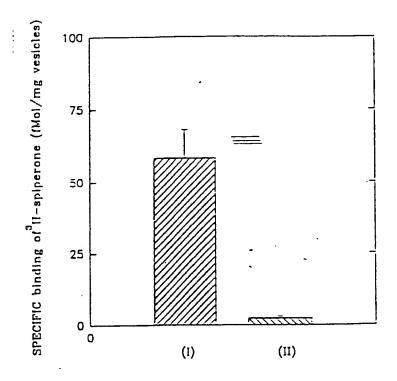


FIGURE 7

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Dictyosculium cNF receptor (RLuin et al., 1988)
Dog adenosine Al receptor (RDC3) (Libert et al., 1989b)
Dog adenosine Al receptor (RDC7) (Libert et al., 1989b)
                     Numan al muscarinic acetylcholine receptor (Peralta ec al., 1987)
                    Numan al muscarinic acetylcholine receptor (veratta et al., 1987)
Numan al muscarinic acetylcholine receptor (Peralta et al., 1987)
Numan mat muscarinic acetylcholine receptor (Peralta et al., 1987)
                      NUMBER NO BUSICALINIC SCHOOLS CHOCKED LUCEPOOR (FOREST NUMBER NO BUSICALINIC SCHOOLS CONTROL FOREST (Bonner et al., 1988)
                      Numan beta 1 adrenergic receptor (Frielle et al., 1987)
                    Numan beta l'adrenergic receptor (Frielle et al., 1987)
Numan bata 2 adrenergic receptor (Nobilka et al., 1987a)
Numan bata 3 adrenergic receptor (Emorine et al., 1989)
Cov alpha 1 adrenergic receptor (Schwinn et al., 1990)
Rat alpha 13 adrenergic receptor (Volgt, et al., 1990)
Numan alpha 2 Cd adrenergic receptor (Ragan et al., 1988)
Numan alpha 2 Cd adrenergic receptor (Komanney et al., 1990)
Numan alpha 2 Clo adrenergic receptor (Kobilka et al., 1990)
Numan alpha 2 adrenergic receptor R20 (Lamier et al., 1991)
Dissophila octopamine receptor (Arakawa et al., 1990)
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                      Nat alpha 2 adrenergic receptor RJO [Lanier et al., 1991)
Drusophila octopamine receptor (Arakawa et al., 1990)
Numan depamine DI receptor [Dearry et al., 1990)
Numan depamine DJ receptor [Sunahara et al., 1991)
Numan depamine DJ receptor (Grandy et al., 1989)
Numan depamine DJ receptor (Girna et al., 1990)
Numan depamine DJ receptor (Cartos et al., 1990)
Numan depamine DJ receptor (ROC4) ( Ramblin and Metcalf, 1991)
Numan serotonin la receptor (ROC4) ( Ramblin and Metcalf, 1991)
Ruman serotonin le receptor (RoC4)
Rat serotonin 2 receptor (Sullius et al., 1988)
Rat serotonin 2 receptor (Sullius et al., 1988)
Numan histamine NZ receptor (Cantz et al., 1991)
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                         Human histamics HZ receptor (Cantz et al., 1991)
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                       Numan N-formyl peptide receptor (Soulay et al., 1990)
Numan Cia anaphylatoxin receptor. (Garard and Garard, 1991)
Numan thrombin receptor (Yu et al., 1991)
Numan thrombin receptor (Yu et al., 1991)
Numan II-8 receptor (Surphy and Liffany, 1991)
Guinea-pig platelet-activating factor receptor (Nonda et al., 1991)
Con emothelin 1 receptor (Arai et al., 1990)
Nat non-isopeptide selective emothelin receptor (Sakurai et al., 1990)
Nat non-isopeptide selective emothelin receptor (Spindal et al., 1991)
Numan vasoactive intestinal peptide receptor (Spindal et al., 1991)
Nat neurosedin B preferring bendmain receptor (Nada et al., 1991)
Nat hradykinin receptor (Tanaka et al., 1990)
Nat hradykinin receptor (Selacharn et al., 1991)
Numan neurokinin A (SK) receptor (Garard et al., 1990)
Numan neurokinin A (SK) receptor (Garard et al., 1990)
Nat meurosedin K receptor (Shiquenoto et al., 1990)
Novine adrenal angiotensin II type-1 receptor (Sasaki et al., 1991)
Numan mas nocopene (angiotensin) receptor (Coung et al., 1986)
                           Numan N-formyl peptide receptor (Souley et al., 1990)
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                               Novan mas oncogene (angiotensin) receptor (Young et al., 1986)
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                               Numan lutropin-choriogonadotropin receptor (Frazier et al., 1990)
Numan thyrotropin receptor (Libert et al., 1989e)
Numan follicle stimulating hormone receptor (Minegish et al., 1991)
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                                 Numan rhodopsin Glachans and Hogness, 1984)
                                 Ruman For opsin (Nathans et al., 1946)
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                                 Ocorant receptor F12 (Buck and Amel, 1991)
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Ocorant receptor I14 (Buck and Amel, 1991)
Coorant receptor I15 (Buck and Amel, 1991)
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                                     Numan cannabinold receptor (Matsuda et al., 1990)
                                     Mouse Glucocorticoid-induced receptor (Marrican et al., 1991)
Rat FCSR (Eva et al., 1990)
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                                    Numan andothelial call GPR Dila and Macing, 1990)
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Rat RGNUT Desperior, DNA and Call Biology, in press, 1991b).
Numan thorsacic aorta GPR (Ross et al., 1990)
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FIGURE 8G

### INTERNATIONAL SEARCH REPORT

Int. ..ional application No. PCT/US93/08528

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	o International Patent Classification (IPC) or to both	national classification and IPC		
B. FIEL	DS SEARCHED			
Minimum de	ocumentation searched (classification system followed	by classification symbols)		
U.S. : 4	435/69.1; 514/12, 13, 14, 15, 16, 17; 530/387.9			
Documentat	ion searched other than minimum documentation to the	extent that such documents are included	in the fields searched	
Electronic d	ata base consulted during the international search (na	me of data base and, where practicable,	search terms used)	
	I/MEDLINE ma: G protein coupled, receptor#, fragment#			
C. DOC	UMENTS CONSIDERED TO BE RELEVANT			
Category*	Citation of document, with indication, where ap	propriate, of the relevant passages	Relevant to claim No.	
A	NATURE, Vol. 336, issued 22 Dece et.al., "Cloning and expression of a cDNA", pages 783-787. See entire do	rat D2 dopamine receptor	1-41	
A	Biochemistry, Vol. 26, No. 10, issued 19 May 1987, H. G. Dohlman et.al., "A Family of Receptors Coupled to Guanine Nucleotide Regulatory Proteins", pages 2657-2664. See entire document.			
Α	BIO/TECHNOLOGY, Vol. 7, issued et.al., "EXPRESSION OF HUMAN & RECEPTORS IN E. COLI AS A N SCREENING", pages 923-927. See e	1 AND 82 ADRENERGIC EW TOOL FOR LIGAND	1-41	
X Further documents are listed in the continuation of Box C. See patent family annex.				
Special categories of cited documents:     T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention.				
1	be part of particular relevance rier decument published on or after the international filing date	"X" document of particular relevance; the		
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